European Journal of Medicinal Chemistry 103 (2015) 506–515

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Short communication

# Synthesis and antibacterial activity of 4″-*O*-(trans-β-arylacrylamido) carbamoyl azithromycin analogs

Mi Yan [a], Xiaodong Ma [a], Ruiqian Dong [b], Xin Li [a], Can Zhao [a], Zhenzhen Guo [a], Yan Shen [a], Fang Liu [a], Ruixin Ma [c], Shutao Ma [a, *]

[a] Department of Medicinal Chemistry, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Shandong University, 44 West Culture Road, Jinan 250012, China
[b] Maternity and Child Care Centre of Jinan, Jinan 250001, China
[c] Affiliated Hospital of Medical College, Qingdao University, Qingdao 266003, China

ARTICLE INFO

*Article history:*
Received 1 July 2015
Received in revised form
11 September 2015
Accepted 13 September 2015
Available online 15 September 2015

*Keywords:*
Antibacterial activity
Bacterial resistance
Evaluation
Synthesis
4″-*O*-(trans-β-arylacrylamido)carbamoyl azithromycin analogs

ABSTRACT

Novel 4″-*O*-(trans-β-arylacrylamido)carbamoyl azithromycin analogs were designed, synthesized and evaluated for their antibacterial activity against nine significant pathogens using broth microdilution method. A majority of these derivatives maintained the activity of azithromycin against susceptible *Streptococcus pyogenes* and all the compounds demonstrated remarkably improved activity compared with the references against all the three phenotypes of resistant *Streptococcus pneumoniae*. In particular, compound **24** exhibited the most potent activity against susceptible *Staphylococcus aureus* (MIC = 0.5 μg/mL), *S. pneumoniae* (MIC = 0.06 μg/mL) and *S. pyogenes* (MIC = 0.25 μg/mL). The most active compound **7** (MIC = 0.015 μg/mL) against resistant *S. pneumoniae* expressing the *mef*A gene, exhibited 512 and 256-fold more potent activity than erythromycin and azithromycin, respectively. Compounds **28** (MIC = 0.5 μg/mL), **29** (MIC = 0.25 μg/mL) and **30** (MIC = 0.5 μg/mL) demonstrated potent activity against resistant *S. pneumoniae* expressing the *erm*B gene, which were 256, 512 and 256-fold better than the references, respectively.



## 1. Introduction

The macrolides are a group of typical antibiotics, the activity of which stems from the macrolide ring, a large lactone ring to which one or more deoxy sugars, usually cladinose or desosamine, are attached [1]. First-generation macrolides, for example, erythromycin A (EMA) (Fig. 1), are widely prescribed for upper and lower respiratory tract infections, particularly for the patients who are drug resistant or allergic to β-lactam antibiotics [2]. Since erythromycin may degrade under acidic conditions losing inherent activity and the degraded products result in undesirable gastrointestinal side effects, second-generation macrolides such as azithromycin (AZM) (Fig. 1) [3,4] and clarithromycin (CAM) (Fig. 1) [5,6] are discovered. However, the emergence of bacterial resistance makes it an urgent need to develop newer generation of macrolides that exhibit significant activity against resistant pathogens [7].

According to the size of the lactone ring, the macrolides are divided into 14-membered, 15-membered and 16-membered compounds [1]. A large number of chemical modifications of 14-membered macrolides have been provided to eliminate antibacterial resistance over the past years. Structure–activity relationships of 14-membered macrolides derivatives lead us to believe that the aryl-alkyl groups attached to the lactone ring or the C-4″ position of the cladinose sugar structure are essential for overcoming macrolide-lincosamide-streptogramin B ($MLS_B$) resistance, whereas the 11,12-cyclic carbamate or the 11,12-cyclic carbonate linkage is important for overcoming efflux resistance. Azithromycin is the first 15-membered macrolide that has a nitrogen atom incorporated into its lactone ring. It shares a similar mechanism of action to the 14-membered macrolides that selectively bind to the 50S subunit of bacterial ribosome resulting in the inhibition of protein synthesis. Since azithromycin is inactive against resistant bacteria, more research is needed to modify its chemical structure to get new analogs with non-cross resistance [8].

The two major mechanisms of macrolide resistance in *Streptococcus pneumonia* are drug efflux pump encoded by the *mef* genes

* Corresponding author.
*E-mail address:* mashutao@sdu.edu.cn (S. Ma).

http://dx.doi.org/10.1016/j.ejmech.2015.09.020
0223-5234/

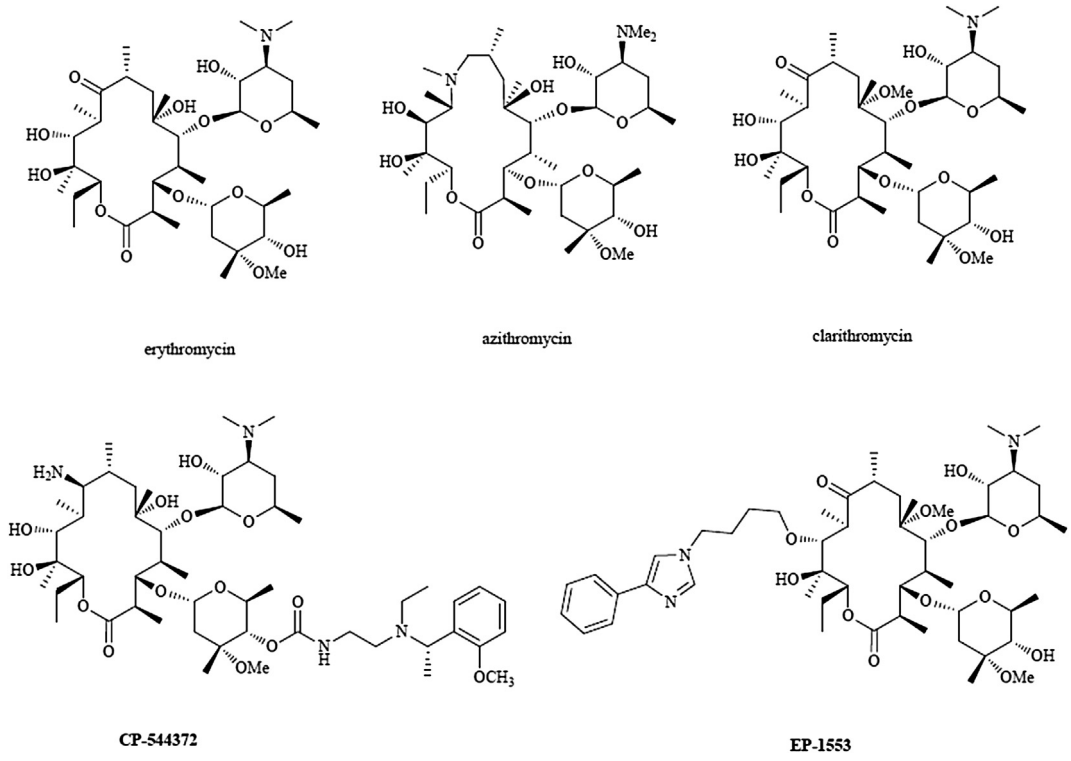



**Fig. 1.** Structures of erythromycin, azithromycin and clarithromycin.

and ribosome methylation resistance encoded by the *erm* genes. The *ermB* gene encodes a methyltransferase, which dimethylates the key nucleotide A2058 in the $MLS_B$ binding site [9]. The previous studies indicated that 11-*O*-arylalkylcarbamoyl group of the macrolide derivatives could interact with A752, and the 4″-*O*-arylalkylcarbamoyl group could interact with nucleotide binding sites between the PTC and the macrolide roadblock. The interactions such as hydrogen bonding, p-stacking and (or) electrostatic force increased affinity for the resistant ribosome, thereby resulting in a remarkable improvement in antibacterial activity against the *Streptococcus pneumoniae* expressing the *erm*B gene. For example, EP-1553 (Fig. 1), an 11-*O*-substituented clarithromycin analog, exhibited fairly good activity against macrolide-resistant *Streptococcus pyogenes, Staphylococcus aureus* and *S. pneumonia* while CP-544372 (Fig. 1) with the C-4″ side chain demonstrated excellent *in vitro* and in vivo activity against susceptible and resistant bacteria.

On the basis of the consideration detailed above, we designed and synthesized a series of novel 4″-*O*-(trans-*β*-arylacrylamido) carbamoyl azithromycin analogs with the 11,12-cyclic carbonate ring or 11-*O*-arylalkylcarbamoyl side chains to enhance their anti-resistant activity and broaden antibacterial spectrum. By introduction of an arylacrylamido group into the 4″-position of 11,12-cyclic carbonate azithromycin, the 4″-*O*-(trans-*β*-arylacrylamido) carbamoyl azithromycin analogs were synthesized. It had been reported that introduction of an arylalkyl group into the 4″-position or the 11-position of 15-membered macrolides enhances antibacterial activity. By introduction of an arylacrylamido group into the 4″-position and C-11 position, the 11,4″-di-*O*-arylalkylcarbamoyl azithromycin analogs were synthesize [8].

## 2. Chemistry

### 2.1. Synthesis of trans-β-arylacryl acids

The synthetic route is outlined in Scheme 1. The reaction of corresponding aldehyde with malonic acid gave trans-*β*-arylacryl acids in the presence of pyridine through the Knoevenagel condensation.

### 2.2. Synthesis of 11,12-cyclic carbonate azithromycin 4″-O-(trans-β-arylacrylamido)carbamoyl analogs

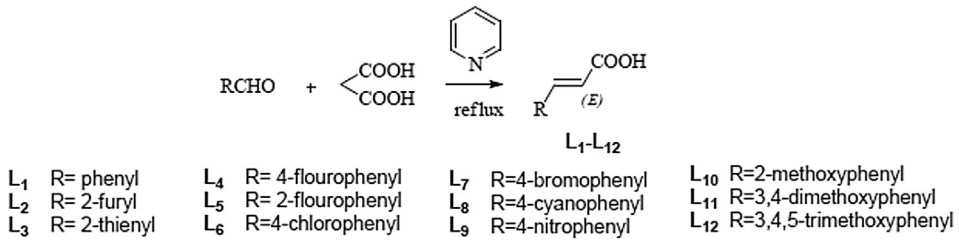
The synthetic method for 11,12-cyclic carbonate azithromycin 4″-*O*-(trans-*β*-arylacrylamido)carbamoyl analogs is shown in Scheme 2. Protection of the 2′-hydroxyl group of azithromycin with acetic anhydride provided 2′-*O*-acetyl product (**2**) [10]. 11,12-Carbonate 2′-*O*-acetyl-4″-*O*-acylimidazolide **3** was prepared in toluene at 55 °C by treatment of **2** with CDI in the presence of triethylamine [8]. Then the acylimidazolide underwent a reaction with hydrazine hydrate (85%), thus affording hydrazide product (**4**). Finally, the hydrazide was converted to 11,12-cyclic carbonate azithromycin 4″-*O*-(trans-β-arylacrylamido)carbamoyl analogs (**5**–**16**) by coupling with various trans-*β*-arylacryl acids in the presence of sodium bicarbonate at 0 °C followed by methanolysis.

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

The 11,12-cyclic carbonate azithromycin 4″-*O*-(trans-β-arylacrylamido)carbamoyl analogs were readily converted to novel 11,4″-di-*O*-arylalkylcarbamoyl azithromycin analogs (**17**–**33**) by reacting with the corresponding amines in the presence of pyridine hydrochloride [8] (Scheme 2).

## 3. Antibacterial evaluation

All the synthesized compounds (**5**–**33**) were determined for their *in vitro* antibacterial activity using the broth microdilution method recommended by NCCL [11]. Minimal inhibitory concentration (MIC) values for all tested compounds were determined in




**Scheme 1.** Synthetic route for $L_1$–$L_{12}$. Regents and Conditions: pyridine, reflux for 12 h.

comparison with azithromycin and clarithromycin on a panel of sensitive and resistant Gram-positive bacterial strains. These strains are *S. aureus* ATCC25923 (erythromycin-susceptible strain), *S. pneumoniae* ATCC49619 (erythromycin-susceptible strain), *S. pyogenes* S2 (erythromycin-susceptible strain isolated clinically), *S. aureus* (penicillin-resistant strain isolated clinically, not characterized), *S. aureus* ATCC29213 (methicillin-resistant strain), *S. pneumoniae* B1 (erythromycin-resistant strain encoded by the *erm* gene), *S. pneumoniae* A22072 (erythromycin-resistant strain encoded by the *mef* gene), *S. pneumoniae* AB11 (erythromycin-resistant strain encoded by the *erm* and *mef* genes), *S. pyogenes* R2 (erythromycin-resistant strain isolated clinically). The MIC results are shown in Table 1.

## 4. Results and discussion

Almost all of the target compounds demonstrated remarkablely improved activity compared with the references against all the three phenotypes of resistant *S. pneumoniae*. Compounds **5**, **10**, **11**, **13**–**16**, **18**–**23** and **26**–**33**, for example, displayed favorable activity against resistant *S. pneumoniae* expressing the *mef*A gene, with MIC values between 0.03 and 0.5 μg/mL. In particular, the most active compound **7** (MIC = 0.015 μg/mL) against resistant *S. pneumoniae* expressing the *mef*A gene, exhibited 512 and 256-fold enhanced activity than EMA and AZM, respectively. Moreover, Compounds **28** (MIC = 0.5 μg/mL), **29** (MIC = 0.25 μg/mL) and **30** (MIC = 0.5 μg/mL) demonstrated potent activity against resistant *S. pneumoniae* expressing the *erm*B gene, which were 256, 512 and 256-fold better than the references, respectively. In remarkable contrast, all of the target compounds displayed weaker activity against penicillin-resistant *S. aureus* than the references and a few of the target compounds such as compounds **17** and **28** maintained the activity of AZM against methicillin-resistant *S. aureus*. As for resistant *S. pneumoniae* expressing the *erm*B and *mef*A genes, compounds **21** and **28**–**30** shared the identical activity with the MIC value of 1 μg/mL, which was 256-fold lower than those of the references.

In addition, most of the target compounds showed improved activity compared with the references against resistant *S. pyogenes*. Particularly, compound **29** had significant activity (MIC = 4 μg/mL) against erythromycin-resistant *S. pyogenes*, showing 32-fold greater activity than the references.

Besides, the 11,4″-di-*O*-arylalkylcarbamoyl analogs **17**–**33** exhibited better activity against penicillin-resistant *S. aureus* and methicillin-resistant *S. aureus* than 11,12-cyclic carbonate 4″-*O*-carbamoyl analogs **5**–**16**. This clearly indicated that the introduction of an arylalkylcarbamoyl group into the 11-position of the 4″-*O*-(trans-β-arylacrylamido)carbamoyl analogs, dramatically enhanced their antibacterial activity against resistant *S. aureus*.

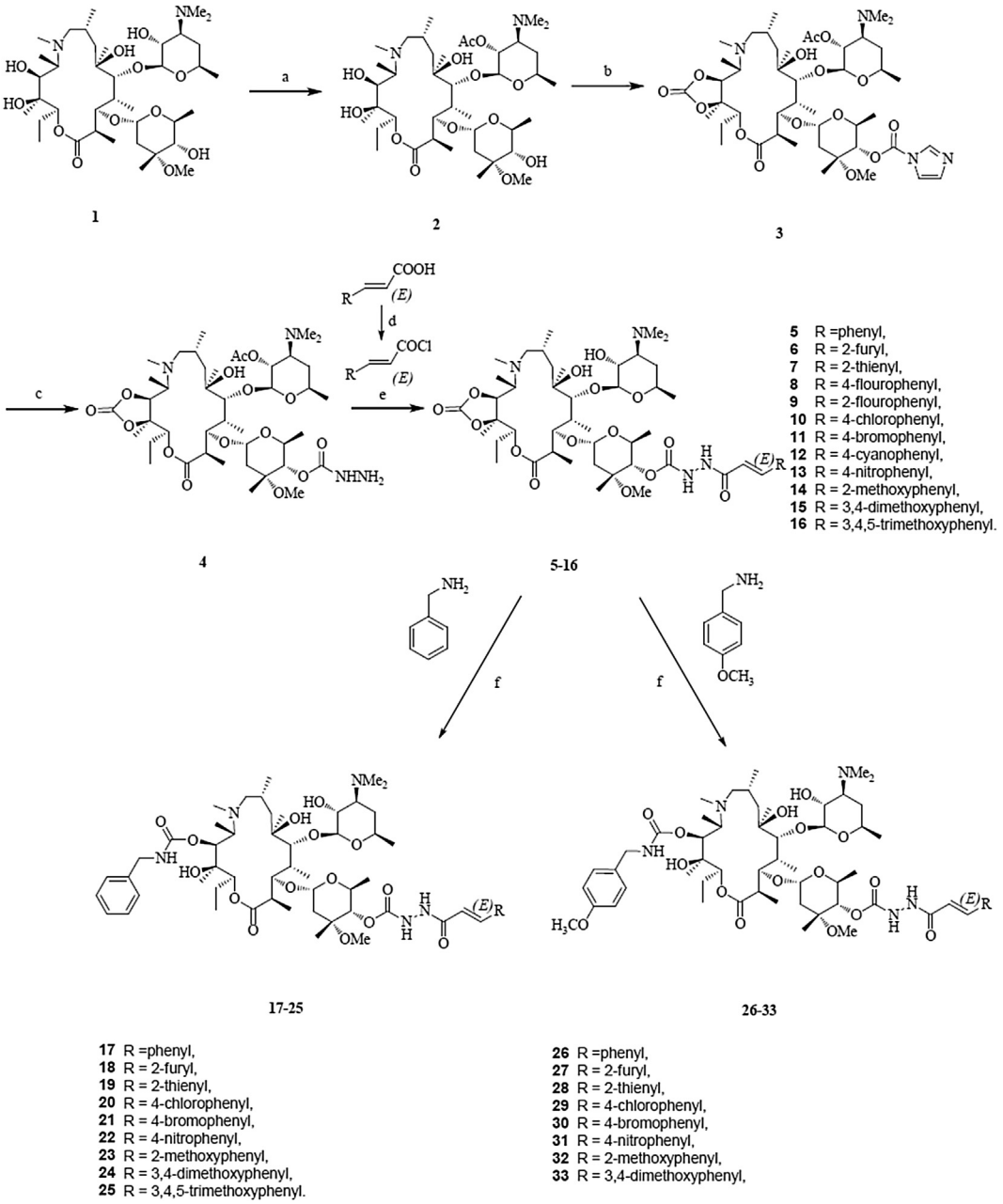
Compounds **5**, **10**, **11**, **13**–**16**, **18**–**23** and **26**–**33** displayed favorable activity against resistant *S. pneumoniae* expressing the *mef*A gene, with MIC values between 0.03 and 0.5 μg/mL. In addition, Compounds **28**, **29** and **30** demonstrated potent activity against resistant *S. pneumoniae* expressing the *erm*B gene, which were 256, 512 and 256-fold better than the references, respectively. We guessed that the 4″-*O*-(trans-β-arylacrylamido)carbamoyl can fit well in the binding pocket of azithromycin in the bacterial ribosome and impart additional affinity to the binding sites, which lead to the restored activity against the erythromycin-susceptible *S. pneumoniae*.

In particular, introduction of the prolonged 4″-*O*-(trans-β-arylacrylamido)carbamoyl group further increased activity against *S. pneumoniae* encoded by the *mef* genes. The prolonged 4″-*O*-(trans-β-arylacrylamido)carbamoyl group with nine atom distances from 4″-oxygen atom to aromatic ring might reach the chloramphenicol-binding sites and interact with them, resulting in better binding to ribosomes in macrolide-resistant bacteria. And the introduction of an arylalkylcarbamoyl group into the 11-position of the 4″-*O*-(trans-β-arylacrylamido)carbamoyl analogs improved their antibacterial activity against resistant bacteria. We speculated that the C-11-arylalkylcarbamoyl side chain interacted with the nucleotide A752 directly in domain II of the 23S rRNA in addition to the main interaction with the nucleotide A2058, which brought about an increased affinity for the resistant ribosome, resulting in superior activity against the resistant *S. pneumoniae*.

On the whole, a majority of the target compounds maintained the activity of AZM against susceptible *S. pyogenes*. Among them, compound **24** exhibited the most potent activity against susceptible *S. aureus* (MIC = 0.5 μg/mL), *S. pneumoniae* (MIC = 0.06 μg/mL) and *S. pyogenes* (MIC = 0.25 μg/mL). In the subseries of compounds **17**–**25**, compound **21** showed the most potent activity against *S. aureus* ATCC25923, *S. pyogenes* S2, *S. pneumoniae* B1, *S. pneumoniae* AB11, *S. pyogenes* R2, respectively, while in the subseries of compounds **26**–**33**, compound **28** displayed the most potent activity against *S. aureus* ATCC25923, *S. pneumoniae* ATCC49619, *S. pyogenes* S2, *S. aureus*, *S. aureus* ATCC29213, *S. pneumoniae* A22072, *S. pneumoniae* AB11, respectively. In addition, 11,4″-di-*O*-arylalkylcarbamoyl analogs (**17**–**33**) displayed MIC values below the susceptible level (MIC ≤ 1 μg/mL) against susceptible *S. aureus* and *S. pneumoniae*, showing better antibacterial activity than 11,12-cyclic carbonate 4″-*O*-arylalkylcarbamoyl analogs (**5**–**16**) against all the three tested susceptible strains. The above results clearly indicated that introduction of arylalkylcarbamoyl group into the 11-position of the 4″-*O*-(trans-β-arylacrylamido)carbamoyl analogs dramatically enhanced their antibacterial activity against susceptible *S. pyogenes*, *S. aureus* and *S. pneumoniae*.

## 5. Conclusions

Novel 4″-*O*-(trans-β-arylacrylamido)carbamoyl azithromycin analogs were designed, synthesized and tested for their *in vitro* antibacterial activity against various phenotypes of Gram-positive and Gram-negative bacteria species [12]. Generally, a majority of




**Scheme 2.** Synthetic route for the synthesis of 4″-*O*-(trans-*β*-arylacrylamido)carbamoyl azithromycin analogs (**5**–**33**). Regents and Conditions: (a) $(CH_3CO)_2O$, $CH_2Cl_2$, $Et_3N$, rt, 24 h; (b) CDI, $Et_3N$, toluene, 55 °C, 72 h; (c) $NH_2NH_2{\cdot}H_2O$ (85%), rt, 0.5 h; (d) $(COCl)_2$, DMF, THF, 0.5 h; (e) $NaHCO_3$, THF, 2 h; $CH_3OH$, 55 °C, 12 h; (f) pyridine hydrochloride, rt, 72 h.

the target compounds maintained the activity of AZM against susceptible *S. pyogenes*, and significantly improved activity compared with the references against resistant *S. pyogenes* and all the three phenotypes of resistant *S. pneumoniae*. Compound **7** was the most active compound (MIC = 0.015 μg/mL) against resistant *S. pneumoniae* expressing the *mef*A gene, exhibited 512 and 256-fold better activity than EMA and AZM, respectively. Compounds **28** (MIC = 0.5 μg/mL), **29** (MIC = 0.25 μg/mL) and **30** (MIC = 0.5 μg/mL) demonstrated potent activity against resistant *S. pneumoniae* expressing the *erm*B gene, which were 256, 512 and 256-fold better than the references, respectively. In addition, 11,4″-*O*-arylalkylcarbamoyl analogs (compound **17**–**33**) showed better antibacterial activity than 11,12-cyclic carbonate 4″-*O*-arylalkylcarbamoyl analogs (compound **5**–**16**) against three susceptible strains of *S. aureus*, *S. pneumoniae* and *S. pyogenes*, penicillin-resistant *S. aureus* and methicillin-resistant *S. aureus*. These findings demonstrated that introduction of an arylalkylcarbamoyl group into the 11-position of the 4″-*O*-(trans-*β*-arylacrylamido)carbamoyl analogs dramatically enhanced their activity against susceptible *S. aureus*, *S. pneumoniae*, *S. pyogenes* and resistant *S. aureus*.

## 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

**Table 1**
4″-*O*-(trans-*β*-arylacrylamido)carbamoyl azithromycin analogs with their *in vitro* antibacterial activity against susceptible and resistant strains (μg/mL).

| Compounds | *S. aureus* ATCC25923[a] | *S. pneumoniae* ATCC49619[b] | *S. pyogenes* S2[c] | *S. aureus*[d] | *S. aureus* ATCC29213[e] | *S. pyogenes* R2[f] | *S. pneumoniae* A22072[g] | *S. pneumoniae* AB11[h] | *S. pyogenes* R2[i] |
|---|---|---|---|---|---|---|---|---|---|
| **5** | 8 | 2 | 0.25 | 8 | 8 | 8 | 0.25 | 4 | 64 |
| **6** | 2 | 8 | 0.25 | 4 | 8 | 32 | 1 | 16 | ≥128 |
| **7** | 32 | 8 | 0.25 | 64 | 64 | 2 | 0.015 | 4 | ≥128 |
| **8** | 2 | 16 | 0.5 | 16 | 8 | 64 | 2 | 16 | 64 |
| **9** | 4 | 8 | 0.25 | 16 | 8 | 16 | 2 | 32 | 64 |
| **10** | 8 | 4 | 1 | 8 | 8 | 8 | 0.5 | 8 | 32 |
| **11** | 4 | 4 | 1 | 8 | 4 | 8 | 0.25 | 4 | 16 |
| **12** | 4 | 16 | 0.5 | 8 | 8 | 64 | 2 | 64 | ≥128 |
| **13** | 2 | 2 | 0.25 | 16 | 8 | 16 | 0.5 | 8 | ≥128 |
| **14** | 2 | 4 | 8 | 8 | 4 | 4 | 0.25 | 2 | 64 |
| **15** | 8 | 2 | 0.5 | 8 | 16 | 32 | 0.5 | 8 | 64 |
| **16** | 8 | 4 | 0.5 | 16 | 16 | 32 | 0.5 | 16 | 64 |
| **17** | 0.5 | 0.5 | 0.5 | 1 | 1 | 2 | 1 | 4 | 32 |
| **18** | 1 | 0.12 | 0.25 | 1 | 4 | 4 | 0.12 | 8 | 64 |
| **19** | 1 | 0.5 | 0.25 | 2 | 4 | 2 | 0.06 | 4 | 32 |
| **20** | 1 | 0.5 | 0.5 | 2 | 4 | 4 | 0.25 | 2 | 16 |
| **21** | 0.5 | 0.25 | 0.25 | 2 | 2 | 1 | 0.12 | 1 | 16 |
| **22** | 0.5 | 0.25 | 0.5 | 2 | 2 | 4 | 0.12 | 2 | 16 |
| **23** | 0.5 | 0.5 | 0.25 | 2 | 2 | 16 | 0.5 | 8 | 32 |
| **24** | 0.5 | 0.06 | 0.25 | 2 | 4 | 64 | 2 | 64 | 64 |
| **25** | 1 | 0.5 | 1 | 4 | 4 | 32 | 2 | 16 | 64 |
| **26** | 1 | 0.25 | 0.25 | 4 | 4 | 2 | 0.25 | 8 | 32 |
| **27** | 1 | 0.5 | 0.25 | 2 | 4 | 2 | 0.25 | 8 | 64 |
| **28** | 0.5 | 0.25 | 0.25 | 2 | 1 | 0.5 | 0.03 | 1 | 32 |
| **29** | 0.5 | 0.5 | 0.5 | 2 | 2 | 0.25 | 0.12 | 1 | 4 |
| **30** | 1 | 0.25 | 0.5 | 2 | 2 | 0.5 | 0.25 | 1 | 16 |
| **31** | 4 | 1 | 0.25 | 8 | 8 | 2 | 0.5 | 8 | 32 |
| **32** | 1 | 0.25 | 0.25 | 4 | 4 | 4 | 0.25 | 8 | 64 |
| **33** | 2 | 0.5 | 0.5 | 4 | 4 | 2 | 0.25 | 8 | 64 |
| EMA | 0.06 | 0.03 | 0.12 | 0.25 | 0.12 | 128 | 8 | 256 | ≥128 |
| AZM | 0.25 | 0.03 | 0.25 | 0.12 | 1 | 128 | 4 | 256 | ≥128 |

[a] *S. aureus* ATCC25923: erythromycin-susceptible strain.
[b] *S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[c] *S. pyogenes* S2: erythromycin-susceptible strain isolated clinically.
[d] *S. aureus*: penicillin-resistant strain isolated clinically, not characterized.
[e] *S. aureus* ATCC29213: methicillin-resistant strain.
[f] *S. pneumoniae* B1: erythromycin-resistant strain encoded by the *erm*B gene.
[g] *S. pneumoniae* A22072: erythromycin-resistant strain encoded by the *mef*A gene.
[h] *S. pneumoniae* AB11: erythromycin-resistant strain encoded by the *erm*B and *mef*A genes.
[i] *S. pyogenes* R2: erythromycin-resistant strain isolated clinically.

Yumingyuan silica gel reagent factory, Shandong, China, YUYUAN). Infrared spectra were recorded on KBr pellets using Nicolet Nexus 470FT-IR spectrometer (Wisconsin, USA). 1H 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). Melting points are uncorrected and were determined on an X-6 melting point apparatus (Beijing Tianchengwode Biotech Co. Ltd, Beijing, China). AZM was used as starting material from Nexchem Pharmaceutical Co. Ltd.

### 6.1. General methods for trans-β-arylacryl acids ($L_1$–$L_{12}$)

To a solution of benzaldehyde (1.06 g, 10 mmol) in pyridine (20 mL) was added malonic acid (2.08 g, 20 mmol). The resulting solution was allowed to stir at 118 °C and reflux for 2 h. Afterward, the solution was concentrated in vacuum to remove pyridine and the residue was quenched with saturated $NaHCO_3$. Washed with ethyl acetate (15mL × 2), the aqueous layer was subsequently adjusted to pH = 1 using concentrated hydrochloric acid and afforded 0.77 g (52%) of L1 as light-yellow precipitates, Rf = 0.30 (petroleum ether/ethyl acetate/acetic acid = 30:10:1). According to the above procedure, corresponding trans-*β*-arylacryl acids **L2**–**L12** were prepared in yields ranging from 52% to 58%.

### 6.2. 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) and $Et_3N$ (1.48 mL, 10.68 mmol). The resulting solution was allowed to stir for 24 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (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 vacuum. The residue was crystallized from acetone–water (2:1) to afford 1.84 g (92%) of 19 as a white solid: mp 167–170 °C; Rf = 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.

### 6.3. 2′-O-acetyl-4″-O-acylimidazolylazithromycin 11,12-cyclic carbonate (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) and CDI (1.23 g, 7.60 mmol). The resulting solution was heated to 55 °C and stirred at the same temperature for 72 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 vacuum. The residue

was purified by flash column chromatography (dichloromethane/methanol, 20:1) to afford 1.61 g (93%) of 20 as a white solid: mp 117–120 °C; Rf = 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.

### 6.4. General methods for the key intermediate (4)

To a solution of **3** (3.0 g, 3.30 mmol) in DMF (20 mL) was added hydrazine hydrate (85%) (0.29 g, 4.95 mmol). The resulting solution was stirred for 0.5 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ 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 vacuum to afford a crude product of 4″-*O*-aminocarbamate **4** (95.6%): Rf = 0.62 (dichloromethane/methanol = 10:1).

### 6.5. General methods for 11,12-cyclic carbonate azithromycin 4″-O-(trans-β-arylacrylamido)carbamoyl analogs (5–16)

To a solution of $\mathbf{L_1}$ (0.41 g, 2.74 mmol) in THF was added oxalyl chloride (1.03 g, 8.22 mmol) drop by drop and DMF (three drops) at 0 °C. The resulting solution was stirred for 0.5 h at the same temperature. Subsequently, the reaction was quenched in vacuum to remove THF and oxalyl chloride and afforded light-yellow residue.

A solution of the key intermediate **4** (3 g, 3.43 mmol) and $NaHCO_3$ (0.23 g, 2.74 mmol) in anhydrous THF was stirred at 0 °C. After addition of the above residue in THF drop by drop, the resulting solution was stirred for another 2 h at the same temperature. Then the reaction was concentrated in vacuum to remove THF and quenched with saturated $NaHCO_3$. Subsequently, the aqueous layer was extracted with ethyl acetate (2 × 25 mL) and the combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated in vacuum to afford a crude product. A solution of the above crude product in methanol was heated to 55 °C and stirred for 12 h at the same temperature. Subsequent concentration of the reaction solution in vacuum provided the crude product of **5**. The above crude product was purified by flash column chromatography eluting with 30:1 dichloromethane/methanol to afford the desired product **5**. According to the above procedure, corresponding compounds **6**–**16** were prepared in yields ranging from 66% to 73%.

### 6.6. General methods for 11,4″-di-O-arylalkylcarbamoyl azithromycin analogs (17–33)

To a solution of **5** (0.50 g, 0.52 mmol) in benzylamine (2.22 mL) was added pyridine hydrochloride (0.17 g, 0.47 mmol). The resulting solution was stirred for 72 h at the room temperature. Afterwards, the reaction was quenched by the addition of ethyl acetate (2 × 15 mL) and saturated $NaH_2PO_4$ (10 mL). Subsequently, the combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated in vacuum to give a crude product, which was subjected to flash column chromatography eluting with 20:1 dichloromethane/methanol to afford the desired product **17**.

According to the above procedure, compounds **18**–**25**, **26**–**33** were prepared in yields ranging from 61% to 73% by condensation of corresponding compounds selected from **5**–**16** with benzyl amine and 4-methoxybenzyl amine respectively.

#### 6.6.1. 4″-O-(Trans-β-phenylacrylamido)carbamoyl azithromycin 11,12-cyclic carbonate (*5*)

White solids, yield 70.8%, mp 158–160 °C, TLC Rf = 0.38 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3596, 3466, 2975, 2939, 2879, 2832, 2788, 1815, 1741, 1685, 1635, 1579, 1461, 1383, 1276, 1219, 1168, 1112, 1045, 1014 cm###1; 1H NMR (600 MHz, $CDCl_3$): 7.69 (d, 1H, J = 15.6 Hz), 7.46–7.45 (m, 2H), 7.36–7.35 (m, 3H), 6.46 (d, 1H, J = 15.6 Hz), 5.07 (s, 1H), 4.89–4.87 (m, 1H), 4.62–4.61 (m, 1H), 4.47–4.41 (m, 4H), 3.68 (s, 1H), 3.60–3.59 (m, 1H), 3.31 (s, 4H), 2.86–2.84 (m, 2H), 2.71 (s, 1H), 2.44–2.32 (m, 8H), 2.21 (s, 3H), 2.07–1.99 (m, 2H), 1.92 (s, 1H), 1.85–1.81 (m, 2H), 1.65–1.55 (m, 3H), 1.44–1.40 (m, 4H), 1.32–1.19 (m, 18H), 1.07–1.04 (m, 7H), 0.99–0.91 (m, 7H); MS (ESI) *m/z* calcd. for $C_{49}H_{78}N_4O_{15}$ 962.5; found ($M + H^+$) 963.9.

#### 6.6.2. 4″-O-[Trans-β-(2-furyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (*6*)

White solids, yield 69.2%, mp 143–146 °C, TLC Rf = 0.41 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3598, 3469, 2973, 2937, 2873, 2789, 1815, 1741, 1681, 1624, 1461, 1382, 1276, 1217, 1167, 1112, 1044 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.95 (d, 1H, J = 15.6 Hz), 7.46–7.45 (m, 1H), 7.34–7.32 (m, 1H), 6.95–6.93 (m, 1H), 6.61 (d, 1H, J = 15.6 Hz), 5.05 (s, 1H), 4.89–4.87 (m, 1H), 4.62–4.60 (m, 1H), 4.51 (d, 1H, J = 5.4 Hz), 4.34–4.31 (m, 3H), 3.72 (s, 1H), 3.60 (d, 1H, J = 5.4 Hz), 3.38–3.36 (m, 1H), 3.28–3.23 (m, 3H), 2.86–2.85 (m, 2H), 2.81 (s, 1H), 2.64–2.57 (m, 5H), 2.44–2.36 (m, 3H), 2.20 (s, 3H), 2.06–2.01 (m, 2H), 1.91 (s, 1H), 1.85–1.81 (m, 2H), 1.66–1.57 (m, 3H), 1.45–1.43 (m, 4H), 1.32–1.17 (m, 18H), 1.08–1.03 (m, 7H), 0.96–0.88 (m, 7H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.25, 153.38, 150.98, 144.51, 129.52, 114.85, 114.61, 112.24, 103.12, 95.32, 85.94, 85.10, 80.59, 78.04, 76.34, 73.52, 73.28, 70.73, 68.48, 67.52, 65.22, 63.00, 61.20, 49.51, 45.28, 43.14, 41.90, 40.25, 35.26, 34.29, 29.01, 26.88, 26.23, 22.08, 22.01, 21.44, 21.02, 17.65, 14.91, 14.14, 10.81, 10.39, 5.49; MS (ESI) *m/z* calcd. for $C_{47}H_{76}N_4O_{16}$ 952.5; found ($M + H^+$) 953.9.

#### 6.6.3. 4″-O-[Trans-β-(2-thienyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (*7*)

White solids, yield 71.2%, mp 149–151 °C, TLC Rf = 0.43 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3597, 3468, 2974, 2937, 2875, 2833, 2788, 1816, 1741, 1682, 1625, 1461, 1383, 1276, 1217, 1168, 1112, 1045, 1014 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.79 (d, 1H, J = 15.6 Hz), 7.35–7.33 (m, 1H), 7.20–7.19 (m, 1H), 7.03–7.01 (m, 1H), 6.26 (d, 1H, J = 15.6 Hz), 5.07 (s, 1H), 4.89–4.88 (m, 1H), 4.62–4.60 (m, 1H), 4.48–4.39 (m, 4H), 3.68 (s, 1H), 3.60–3.59 (m, 1H), 3.31 (s, 4H), 2.89–2.86 (m, 2H), 2.73 (s, 1H), 2.44–2.36 (m, 8H), 2.20 (s, 3H), 2.06–2.00 (m, 2H), 1.91 (s, 1H), 1.85–1.80 (m, 2H), 1.66–1.60 (m, 3H), 1.44–1.37 (m, 4H), 1.33–1.19 (m, 18H), 1.07–1.06 (m, 7H), 0.94–0.86 (m, 7H); MS (ESI) *m/z* calcd. for $C_{47}H_{76}N_4O_{15}S$ 968.5; found ($M + H^+$) 969.8.

#### 6.6.4. 4″-O-[Trans-β-(4-flourophenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (*8*)

White solids, yield 70.3%, mp 162–165 °C, TLC Rf = 0.37 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3600, 3530, 3273, 2972, 2933, 2857, 2787, 1816, 1740, 1679, 1635, 1601, 1461, 1382, 1230, 1166, 1111, 1045 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.62 (d, 1H, J = 15.6 Hz), 7.44–7.43 (m, 2H), 7.04–7.02 (m, 2H), 6.41 (d, 1H, J = 15.6 Hz), 5.06 (s, 1H), 4.88–4.87 (m, 1H), 4.61–4.60 (m, 1H), 4.41–4.37 (m, 4H), 3.70–3.67 (m, 1H), 3.59 (s, 1H), 3.35–3.31 (m, 4H), 2.87–2.84 (m, 2H), 2.83 (s, 1H), 2.58–2.35 (m, 8H), 2.21 (s, 3H), 2.03–1.78 (m, 5H), 1.66–1.56 (m, 3H), 1.47–1.41 (m, 4H), 1.34–1.22 (m, 18H), 1.08–1.05 (m, 7H), 0.95–0.91 (m, 7H); MS (ESI) *m/z* calcd. for $C_{49}H_{77}FN_4O_{15}$ 980.5; found ($M + H^+$) 982.1.

#### 6.6.5. 4″-O-[Trans-β-(2-flourophenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (*9*)

White solids, yield 65.7%, mp 159–163 °C, TLC Rf = 0.44 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3599, 3524, 3294, 2975, 2940,

2879, 2832, 2789, 1816, 1741, 1689, 1636, 1579, 1460, 1383, 1230, 1168, 1111, 1045, 1015 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.78 (d, 1H, J = 15.6 Hz), 7.46–7.45 (m, 1H), 7.33–7.32 (m, 1H), 7.14–7.12 (m, 1H), 7.07–7.04 (m, 1H), 6.59 (d, 1H, J = 15.6 Hz), 5.08 (s, 1H), 4.89–4.88 (m, 1H), 4.62–4.61 (m, 1H), 4.47–4.42 (m, 4H), 3.67 (s, 1H), 3.60–3.59 (m, 1H), 3.35–3.25 (m, 4H), 2.86–2.85 (m, 2H), 2.65 (s, 1H), 2.44–2.37 (m, 8H), 2.20 (s, 3H), 2.07–1.99 (m, 2H), 1.91 (s, 1H), 1.85–1.80 (m, 2H), 1.66–1.56 (m, 3H), 1.48–1.40 (m, 4H), 1.33–1.19 (m, 18H), 1.07–1.05 (m, 7H), 0.93–0.90 (m, 7H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.20, 162.65, 160.13, 153.39, 135.92, 131.42, 129.48, 124.44, 119.85, 116.22, 116.00, 103.21, 95.37, 85.90, 85.13, 80.83, 78.06, 76.32, 73.49, 73.2, 70.77, 68.54, 67.55, 65.26, 62.98, 61.20, 49.53, 45.29, 43.20, 41.89, 40.28, 35.29, 34.31, 28.91, 26.87, 26.25, 22.09, 22.01, 21.48, 21.03, 17.66, 14.90, 14.18, 10.83, 10.40, 5.53; MS (ESI) *m/z* calcd. for $C_{49}H_{77}FN_4O_{15}$ 980.5; found ($M + H^+$) 981.9.

#### 6.6.6. 4″-O-[Trans-β-(4-chlorophenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (**10**)

White solids, yield 71.1%, mp 161–163 °C, TLC Rf = 0.43 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3596, 3524, 3271, 2975, 2939, 2879, 2832, 2788, 1815, 1741, 1678, 1634, 1593, 1461, 1383, 1220, 1168, 1111, 1045 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.56 (d, 1H, J = 15.6 Hz), 7.35–7.34 (m, 2H), 7.32–7.30 (m, 2H), 6.48 (d, 1H, J = 15.6 Hz), 5.07 (s, 1H), 4.89–4.86 (m, 1H), 4.62–4.60 (m, 1H), 4.49–4.35 (m, 4H), 3.68 (s, 1H), 3.59 (s, 1H), 3.31–3.26 (m, 4H), 2.89–2.83 (m, 2H), 2.73 (s, 1H), 2.44–2.34 (m, 8H), 2.23–2.21 (m, 3H), 2.07–1.99 (m, 2H), 1.92 (s, 1H), 1.85–1.80 (m, 2H), 1.65–1.56 (m, 3H), 1.46–1.39 (m, 4H), 1.36–1.18 (m, 18H), 1.12–1.05 (m, 7H), 0.98–0.90 (m, 7H); MS (ESI) *m/z* calcd. for $C_{49}H_{77}ClN_4O_{15}$ 996.5; found ($M + H^+$) 998.0.

#### 6.6.7. 4″-O-[Trans-β-(4-bromophenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (**11**)

White solids, yield 73.2%, mp 162–165 °C, TLC Rf = 0.36 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3595, 3525, 2974, 2938, 2879, 2831, 2788, 1815, 1740, 1685, 1634, 1588, 1461, 1383, 1264, 1220, 1168, 1111, 1072, 1045 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.57 (d, 1H, J = 15.6 Hz), 7.47–7.45 (m, 2H), 7.28–7.27 (m, 2H), 6.46 (d, 1H, J = 15.6 Hz), 5.08 (s, 1H), 4.89–4.87 (m, 1H), 4.62–4.60 (m, 1H), 4.48–4.43 (m, 4H), 3.68–3.66 (m, 1H), 3.61–3.59 (m, 1H), 3.33–3.31 (m, 4H), 2.88–2.83 (m, 2H), 2.65 (s, 1H), 2.40–2.31 (m, 8H), 2.21 (s, 3H), 2.07–1.99 (m, 2H), 1.92 (s, 1H), 1.85–1.81 (m, 2H), 1.66–1.54 (m, 3H), 1.45–1.39 (m, 4H), 1.33–1.19 (m, 18H), 1.07–1.03 (m, 7H), 0.99–0.90 (m, 7H); MS (ESI) *m/z* calcd. for $C_{49}H_{77}BrN_4O_{15}$ 1040.5; found ($M + H^+$) 1043.7.

#### 6.6.8. 4″-O-[Trans-β-(4-cyanophenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (**12**)

White solids, yield 67.9%, mp 164–166 °C, TLC Rf = 0.42 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3596, 3525, 2975, 2939, 2880, 2832, 2788, 2229, 1814, 1740, 1685, 1637, 1605, 1461, 1384, 1274, 1223, 1169, 1112, 1044 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.65–7.62 (m, 2H), 7.60–7.58 (m, 2H), 7.54–7.52 (m, 1H), 6.63–6.61 (m, 1H), 5.05–5.04 (m, 1H), 4.89–4.86 (m, 1H), 4.60–4.56 (m, 2H), 4.43–4.30 (m, 3H), 3.74–3.71 (m, 1H), 3.59–3.57 (m, 1H), 3.48–3.44 (m, 1H), 3.33 (s, 3H), 3.30 (s, 1H), 2.96 (s, 1H), 2.89–2.77 (m, 8H), 2.47–2.44 (m, 1H), 2.39–2.36 (m, 1H), 2.22 (s, 3H), 2.15–1.80 (m, 6H), 1.64–1.56 (m, 3H), 1.51–0.82 (m, 34H); MS (ESI) *m/z* calcd. for $C_{50}H_{77}N_5O_{15}$ 987.5; found ($M + H^+$) 988.9.

#### 6.6.9. 4″-O-[Trans-β-(4-nitrophenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (**13**)

Yellow solids, yield 68.5%, mp 138–140 °C, TLC Rf = 0.45 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3598, 3526, 2975, 2939, 2878, 2832, 2788, 1815, 1741, 1689, 1637, 1599, 1461, 1383, 1275, 1220, 1168, 1111, 1045, 1014 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 8.21–8.19 (m, 2H), 7.67–7.64 (m, 1H), 7.59–7.57 (m, 2H), 6.65–6.63 (m, 1H), 5.09 (s, 1H), 4.89 (d, 1H, J = 9.6 Hz), 4.63 (d, 1H, J = 9.6 Hz), 4.46–4.41 (m, 4H), 3.66 (s, 1H), 3.60–3.58 (m, 1H), 3.34–3.28 (m, 4H), 2.89–2.85 (m, 2H), 2.66 (s, 1H), 2.45–2.35 (m, 8H), 2.21 (s, 3H), 2.08–2.00 (m, 2H), 1.93 (m, 1H), 1.85–1.80 (m, 2H), 1.67–1.55 (m, 3H), 1.47–1.37 (m, 4H), 1.33–1.15 (m, 18H), 1.09–0.90 (m, 14H); MS (ESI) *m/z* calcd. for $C_{49}H_{77}N_5O_{17}$ 1007.5; found ($M + H^+$) 1008.9.

#### 6.6.10. 4″-O-[Trans-β-(2-methoxyphenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (**14**)

Light-yellow solids, yield 72.3%, mp 156–159 °C, TLC Rf = 0.43 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3598, 3524, 2973, 2937, 2877, 2788, 1815, 1741, 1685, 1629, 1578, 1463, 1383, 1220, 1167, 1111, 1046 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.47–7.45 (m, 2H), 6.82–6.78 (m, 1H), 6.57–6.55 (m, 1H), 6.46–6.43 (m, 1H), 6.38–6.34 (m, 1H), 5.07 (s, 1H), 4.89–4.87 (m, 1H), 4.62–4.59 (m, 1H), 4.48–4.41 (m, 4H), 3.83 (s, 3H), 3.67 (s, 1H), 3.60–3.58 (m, 1H), 3.34–3.31 (m, 4H), 2.89–2.85 (m, 2H), 2.69 (s, 1H), 2.54–2.27 (m, 8H), 2.22 (s, 3H), 2.08–1.96 (m, 2H), 1.91 (s, 1H), 1.85–1.80 (m, 2H), 1.68–1.51 (m, 3H), 1.48–1.35 (m, 4H), 1.34–0.80 (m, 32H); MS (ESI) *m/z* calcd. for $C_{50}H_{80}N_4O_{16}$ 992.6; found ($M + H^+$) 993.9.

#### 6.6.11. 4″-O-[Tans-β-(3,4-dimethoxyphenyl)acrylamido]carbamoyl azithromycin 11,12-cyclic carbonate (**15**)

White solids, yield 69.5%, mp 155–159 °C, TLC Rf = 0.41 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3598, 3525, 3341, 2972, 2921, 2850, 2788, 1815, 1741, 1685, 1631, 1464, 1383, 1263, 1219, 1167, 1112, 1045 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.57 (d, 1H, J = 15.6 Hz), 7.00 (d, 1H, J = 9.0 Hz), 6.93 (s, 1H), 6.81 (d, 1H, J = 9.0 Hz), 6.46 (d, 1H, J = 15.6 Hz), 5.10 (s, 1H), 4.91–4.87 (m, 1H), 4.62–4.60 (m, 1H), 4.48–4.40 (m, 4H), 3.93–3.76 (m, 6H), 3.67 (s, 1H), 3.63–3.55 (m, 1H), 3.36–3.27 (m, 4H), 2.87–2.85 (m, 2H), 2.67 (s, 1H), 2.44–2.32 (m, 8H), 2.21–2.17 (m, 3H), 2.08–1.96 (m, 2H), 1.92 (s, 1H), 1.85–1.80 (m, 2H), 1.65–1.55 (m, 3H), 1.45–1.39 (m, 4H), 1.34–1.16 (m, 18H), 1.13–0.82 (m, 14H); MS (ESI) *m/z* calcd. for $C_{51}H_{82}N_4O_{17}$ 1022.6; found ($M + H^+$) 1024.1.

#### 6.6.12. 4″-O-[Trans-β-(3,4,5-trimethoxyphenyl)acrylamido] carbamoyl azithromycin 11,12-cyclic carbonate (**16**)

White solids, yield 71.6%, mp 154–157 °C, TLC Rf = 0.43 ($CH_2Cl_2$:MeOH = 10:1); IR (KBr): 3598, 3525, 3306, 2973, 2939, 2876, 2836, 2788, 1815, 1741, 1678, 1633, 1583, 1461, 1383, 1268, 1219, 1168, 1045, 1013 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.45 (d, 1H, J = 15.6 Hz), 6.57 (s, 2H), 6.34 (d, 1H, J = 15.6 Hz), 5.09 (s, 1H), 4.88–4.86 (m, 1H), 4.62–4.60 (m, 1H), 4.49–4.45 (m, 4H), 3.86–3.83 (m, 9H), 3.62 (s, 1H), 3.60–3.58 (m, 1H), 3.35–3.27 (m, 4H), 2.88–2.85 (m, 2H), 2.64 (s, 1H), 2.44–2.33 (m, 8H), 2.21 (s, 3H), 2.08–2.00 (m, 2H), 1.92 (s, 1H), 1.84–1.76 (m, 2H), 1.68–1.58 (m, 3H), 1.48–1.38 (m, 4H), 1.33–1.19 (m, 18H), 1.08–0.90 (m, 14H); MS (ESI) *m/z* calcd. for $C_{52}H_{84}N_4O_{18}$ 1052.6; found ($M + H^+$) 1054.0.

#### 6.6.13. 4″-O-(Trans-β-phenylacrylamido)carbamoyl-11-O-benzyl carbamoyl azithromycin (**17**)

White solids, yield 73.1%, mp 155–157 °C, TLC Rf = 0.20 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3459, 3311, 2974, 2937, 2875, 2789, 1732, 1635, 1528, 1456, 1382, 1170, 1112, 1045, 1015 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.75–7.70 (m, 1H), 7.55–7.50 (m, 2H), 7.42–7.40 (m, 2H), 7.35–7.33 (m, 3H), 7.24–7.22 (m, 3H), 6.52–6.50 (m, 1H), 5.07–5.05 (m, 1H), 4.97 (s, 1H), 4.85 (s, 1H), 4.51–4.43 (m, 3H), 4.33–4.31 (m, 1H), 3.73–3.72 (m, 2H), 3.67 (s, 2H), 3.36–3.27 (m, 4H), 3.25 (s, 2H), 2.63–2.55 (m, 3H), 2.36–2.33 (m, 6H), 2.29 (s, 3H), 2.17–2.15 (m, 2H), 2.03 (s, 2H), 1.97–1.88 (m, 3H), 1.76–1.75 (m, 1H), 1.63 (s, 2H), 1.58–1.55 (m, 2H), 1.47 (s, 1H), 1.33–0.87 (m, 33H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 176.62, 143.03, 138.88, 134.47, 130.93,

130.09, 128.88, 128.84, 128.62, 128.50, 128.03, 126.51, 126.38, 117.26, 104.01, 96.40, 80.44, 79.23, 75.28, 73.91, 73.21, 70.57, 68.90, 65.22, 63.38, 61.97, 49.66, 45.63, 42.98, 42.37, 41.76, 40.36, 36.00, 35.51, 30.57, 29.63, 27.48, 26.24, 21.77, 21.22, 21.02, 19.18, 17.39, 14.41, 11.46, 10.61, 9.79; MS (ESI) *m/z* calcd. for $C_{56}H_{87}N_5O_{15}$ 1069.6; found ($M + H^+$) 1070.9.

*6.6.14. 4″-O-[Trans-β-(2-furyl)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**18**)*

White solids, yield 65.4%, mp 141–144 °C, TLC Rf = 0.23 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3311, 2974, 2936, 1812, 1731, 1639, 1529, 1456, 1382, 1168, 1110, 1074, 1043, 1015 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.80–7.76 (m, 1H), 7.45–7.39 (m, 2H), 7.37–7.30 (m, 5H), 6.46–6.42 (m, 1H), 6.38–6.35 (m, 1H), 5.09 (s, 1H), 4.99–4.97 (m, 1H), 4.82 (s, 1H), 4.53–4.47 (m, 3H), 4.31–4.28 (m, 1H), 3.70–3.69 (m, 2H), 3.63 (s, 2H), 3.30–3.21 (m, 4H), 3.18 (s, 2H), 2.61–2.57 (m, 3H), 2.37–2.34 (m, 6H), 2.30 (s, 3H), 2.18–2.16 (m, 2H), 1.98 (s, 2H), 1.94–1.86 (m, 3H), 1.74–1.73 (m, 1H), 1.61 (s, 2H), 1.56–1.53 (m, 2H), 1.43 (s, 1H), 1.35–0.90 (m, 33H); MS (ESI) *m/z* calcd. for $C_{54}H_{85}N_5O_{16}$ 1059.6; found ($M + H^+$) 1061.4.

*6.6.15. 4″-O-[Trans-β-(2-thienyl)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**19**)*

White solids, yield 70.5%, mp 146–150 °C, TLC Rf = 0.18 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3322, 2973, 2936, 1814, 1733, 1624, 1521, 1458, 1380, 1168, 1112, 1045 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.85–7.83 (m, 1H), 7.77–7.75 (m, 1H), 7.57–7.55 (m, 1H), 7.53–7.51 (m, 1H), 7.32–7.30 (m, 2H), 7.26–7.24 (m, 3H), 6.89–6.86 (m, 1H), 5.05 (s, 1H), 4.95–4.93 (m, 1H), 4.79 (s, 1H), 4.48–4.43 (m, 3H), 4.27–4.25 (m, 1H), 3.65–3.64 (m, 2H), 3.58 (s, 2H), 3.25–3.19 (m, 4H), 3.16 (s, 2H), 2.58–2.55 (m, 3H), 2.34–2.31 (m, 6H), 2.28 (s, 3H), 2.16–2.13 (m, 2H), 1.96 (s, 2H), 1.91–1.83 (m, 3H), 1.76–1.73 (m, 1H), 1.58 (s, 2H), 1.53–1.51 (m, 2H), 1.41 (s, 1H), 1.37–0.89 (m, 33H); MS (ESI) *m/z* calcd. for $C_{54}H_{85}N_5O_{15}S$ 1075.6; found ($M + H^+$) 1077.2.

*6.6.16. 4″-O-[Trans-β-(4-chloropheny)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**20**)*

White solids, yield 71.4%, mp 156–158 °C, TLC Rf = 0.22 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3461, 3316, 2975, 2937, 2876, 2832, 2788, 1815, 1733, 1635, 1592, 1458, 1382, 1169, 1112, 1045, 1014 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.65–7.63 (m, 1H), 7.60–7.58 (m, 2H), 7.43–7.41 (m, 2H), 7.31–7.30 (m, 2H), 7.26–7.23 (m, 3H), 6.53–6.38 (m, 1H), 5.02–5.00 (m, 1H), 4.94 (s, 1H), 4.83 (s, 1H), 4.50–4.40 (m, 3H), 4.30–4.28 (m, 1H), 3.73–3.72 (m, 2H), 3.63 (s, 2H), 3.35–3.25 (m, 4H), 3.21 (s, 2H), 2.61–2.52 (m, 3H), 2.35–2.31 (m, 6H), 2.25 (s, 3H), 2.18–2.16 (m, 2H), 2.01 (s, 2H), 1.95–1.85 (m, 3H), 1.74–1.72 (m, 1H), 1.60 (s, 2H), 1.52–1.50 (m, 2H), 1.44 (s, 1H), 1.30–0.90 (m, 33H); MS (ESI) *m/z* calcd. for $C_{56}H_{86}ClN_5O_{15}$ 1103.6; found ($M + H^+$) 1105.4.

*6.6.17. 4″-O-[Trans-β-(4-bromophenyl)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**21**)*

White solids, yield 70.6%, mp 158–160 °C, TLC Rf = 0.22 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3455, 2973, 2933, 1814, 1732, 1635, 1587, 1458, 1381, 1169, 1112, 1045 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.65–7.62 (m, 2H), 7.51–7.48 (m, 2H), 7.39–7.37 (m, 1H), 7.33–7.31 (m, 2H), 7.24–7.21 (m, 3H), 6.79–6.77 (m, 1H), 5.08 (s, 1H), 4.95 (s, 1H), 4.79 (s, 1H), 4.52–4.43 (m, 3H), 4.25–4.23 (m, 1H), 3.68–3.66 (m, 2H), 3.64 (s, 2H), 3.38–3.31 (m, 4H), 3.22 (s, 2H), 2.59–2.53 (m, 3H), 2.35–2.31 (m, 6H), 2.26 (s, 3H), 2.18–2.16 (m, 2H), 2.04 (s, 2H), 1.99–1.89 (m, 3H), 1.73–1.72 (m, 1H), 1.56 (s, 2H), 1.53–1.51 (m, 2H), 1.42 (s, 1H), 1.21–0.91 (m, 33H); MS (ESI) *m/z* calcd. for $C_{56}H_{86}BrN_5O_{15}$ 1147.5; found ($M + H^+$) 1148.8.

*6.6.18. 4″-O-[Trans-β-(4-nitrophenyl)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**22**)*

White solids, yield 69.8%, mp 143–145 °C, TLC Rf = 0.20 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3323, 2974, 1813, 1731, 1637, 1599, 1522, 1458, 1381, 1344, 1169, 1111, 1043 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 8.24–8.21 (m, 3H), 7.76–7.72 (m, 2H), 7.31–7.30 (m, 2H), 7.23–7.20 (m, 3H), 7.11–7.09 (m, 1H), 5.08 (s, 1H), 4.96 (s, 1H), 4.82 (s, 1H), 4.52–4.46 (m, 3H), 4.28–4.26 (m, 1H), 3.70–3.68 (m, 2H), 3.66 (s, 2H), 3.40–3.34 (m, 4H), 3.24 (s, 2H), 2.61–2.55 (m, 3H), 2.33–2.30 (m, 6H), 2.24 (s, 3H), 2.15–2.13 (m, 2H), 2.00 (s, 2H), 1.98–1.87 (m, 3H), 1.71–1.70 (m, 1H), 1.57 (s, 2H), 1.55–1.53 (m, 2H), 1.43 (s, 1H), 1.28–0.93 (m, 33H); MS (ESI) *m/z* calcd. for $C_{56}H_{86}N_6O_{17}$ 1114.6; found ($M + H^+$) 1116.2.

*6.6.19. 4″-O-[Trans-β-(2-methoxyphenyl)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**23**)*

White solids, yield 70.3%, mp 153–155 °C, TLC Rf = 0.19 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3309, 2975, 2937, 2836, 1812, 1730, 1642, 1578, 1517, 1455, 1382, 1344, 1168, 1123, 1045 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.95 (d, 1H, J = 15.6 Hz), 7.78–7.76 (m, 1H), 7.38–7.34 (m, 3H), 7.22–7.16 (m, 2H), 7.02–6.76 (m, 3H), 6.60 (d, 1H, J = 15.6 Hz), 5.06 (s, 1H), 4.99 (s, 1H), 4.85 (s, 1H), 4.53–4.48 (m, 3H), 4.30–4.28 (m, 1H), 3.83–3.80 (m, 3H), 3.71–3.69 (m, 2H), 3.63 (s, 2H), 3.37–3.34 (m, 4H), 3.20 (s, 2H), 2.57–2.54 (m, 3H), 2.30–2.27 (m, 6H), 2.23 (s, 3H), 2.11–2.09 (m, 2H), 1.99 (s, 2H), 1.96–1.89 (m, 3H), 1.70–1.68 (m, 1H), 1.55 (s, 2H), 1.53–1.51 (m, 2H), 1.45 (s, 1H), 1.27–0.98 (m, 33H); MS (ESI) *m/z* calcd. for $C_{57}H_{89}N_5O_{16}$ 1099.6; found ($M + H^+$) 1101.1.

*6.6.20. 4″-O-[Trans-β-(3,4-dimethoxyphenyl)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**24**)*

White solids, yield 72.4%, mp 152–154 °C, TLC Rf = 0.20 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3463, 2973, 2936, 1815, 1734, 1632, 1600, 1516, 1459, 1383, 1343, 1167, 1112, 1046 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.36–7.33 (m, 3H), 7.26–7.23 (m, 4H), 7.18–7.16 (m, 1H), 6.88–6.87 (m, 2H), 5.09–5.07 (m, 1H), 4.95 (s, 1H), 4.87 (s, 1H), 4.55–4.50 (m, 3H), 4.33–4.31 (m, 1H), 3.82–3.81 (m, 6H), 3.73–3.71 (m, 2H), 3.66 (s, 2H), 3.39–3.36 (m, 4H), 3.22 (s, 2H), 2.55–2.53 (m, 3H), 2.31–2.29 (m, 6H), 2.25 (s, 3H), 2.10–2.07 (m, 2H), 1.98 (s, 2H), 1.93–1.83 (m, 3H), 1.72–1.71 (m, 1H), 1.57 (s, 2H), 1.55–1.53 (m, 2H), 1.49 (s, 1H), 1.25–0.99 (m, 33H); MS (ESI) *m/z* calcd. for $C_{58}H_{91}N_5O_{17}$ 1129.6; found ($M + H^+$) 1131.4.

*6.6.21. 4″-O-[Trans-β-(3,4,5-trimethoxyphenyl)acrylamido]carbamoyl-11-O-benzyl carbamoyl azithromycin (**25**)*

White solids, yield 70.2%, mp 151–154 °C, TLC Rf = 0.18 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3501, 3308, 2975, 2937, 2835, 1812, 1731, 1641, 1583, 1504, 1456, 1382, 1328, 1168, 1043, 1011 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.42–7.40 (m, 3H), 7.32–7.29 (m, 3H), 6.90–6.88 (m, 1H), 6.80 (s, 2H), 5.06 (s, 1H), 4.97–4.95 (m, 1H), 4.85 (s, 1H), 4.53–4.50 (m, 3H), 4.30–4.29 (m, 1H), 3.80 (m, 9H), 3.73–3.71 (m, 2H), 3.64 (s, 2H), 3.37–3.35 (m, 4H), 3.26 (s, 2H), 2.57–2.55 (m, 3H), 2.30–2.28 (m, 6H), 2.25 (s, 3H), 2.09–2.06 (m, 2H), 1.95 (s, 2H), 1.90–1.80 (m, 3H), 1.73–1.72 (m, 1H), 1.55 (s, 2H), 1.51–1.49 (m, 2H), 1.45 (s, 1H), 1.33–1.00 (m, 33H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 176.67, 153.34, 139.87, 138.98, 137.79, 130.08, 128.87, 128.70, 128.48, 127.54, 126.71, 126.35, 105.27, 103.76, 96.25, 80.34, 79.20, 75.18, 74.02, 73.31, 70.54, 68.74, 65.19, 62.09, 61.76, 60.93, 56.17, 49.64, 45.68, 42.41, 40.29, 35.99, 31.72, 29.66, 27.32, 26.33, 21.89, 21.21, 21.03, 19.25, 17.45, 14.50, 11.38, 10.37, 9.78; MS (ESI) *m/z* calcd. for $C_{59}H_{93}N_5O_{18}$ 1159.7; found ($M + H^+$) 1161.0.

*6.6.22. 4″-O-(Trans-β-phenylacrylamido)carbamoyl-11-O-(4-methoxybenzyl)carbamoyl azithromycin (**26**)*

White solids, yield 71.2%, mp 146–149 °C, TLC Rf = 0.25

($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3321, 2974, 2835, 1812, 1731, 1638, 1608, 1580, 1513, 1461, 1381, 1340, 1170, 1110, 1036 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.72–7.67 (m, 2H), 7.48–7.44 (m, 2H), 7.37–7.32 (m, 2H), 7.28–7.22 (m, 2H), 6.89–6.80 (m, 3H), 5.02–5.00 (m, 1H), 4.93–4.92 (m, 1H), 4.65 (s, 1H), 4.43–4.34 (m, 3H), 4.24–4.22 (m, 1H), 3.84–3.82 (m, 3H), 3.67–3.65 (m, 2H), 3.57 (s, 2H), 3.29–3.21 (m, 4H), 3.17–3.15 (m, 2H), 2.55–2.50 (m, 3H), 2.29–2.23 (m, 6H), 2.19 (s, 3H), 2.12–2.10 (m, 2H), 2.01 (s, 2H), 1.89–1.82 (m, 3H), 1.68–1.66 (m, 1H), 1.58 (s, 2H), 1.49–1.47 (m, 2H), 1.40 (s, 1H), 1.33–0.88 (m, 33H); MS (ESI) *m/z* calcd. for $C_{57}H_{89}N_5O_{16}$ 1099.6; found ($M + H^+$) 1101.3.

*6.6.23. 4″-O-[Trans-β-(2-furyl)acrylamido]carbamoyl-11-O-(4-methoxybenzyl)carbamoyl azithromycin (**27**)*

White solids, yield 68.4%, mp 133–137 °C, TLC Rf = 0.25 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3321, 2973, 2937, 2836, 1811, 1730, 1637, 1608, 1579, 1513, 1462, 1382, 1338, 1168, 1110, 1035 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.47–7.45 (m, 2H), 7.24–7.22 (m, 3H), 6.89–6.87 (m, 2H), 6.59–6.57 (m, 1H), 6.47–6.45 (m, 1H), 5.04–5.02 (m, 1H), 4.96–4.94 (m, 1H), 4.68 (s, 1H), 4.45–4.38 (m, 3H), 4.25–4.22 (m, 1H), 3.86–3.84 (m, 3H), 3.68–3.66 (m, 2H), 3.59 (s, 2H), 3.28–3.23 (m, 4H), 3.18–3.15 (m, 2H), 2.54–2.51 (m, 3H), 2.31–2.25 (m, 6H), 2.21 (s, 3H), 2.11–2.08 (m, 2H), 2.03 (s, 2H), 1.87–1.83 (m, 3H), 1.67–1.65 (m, 1H), 1.56 (s, 2H), 1.48–1.45 (m, 2H), 1.38 (s, 1H), 1.30–0.85 (m, 33H); MS (ESI) *m/z* calcd. for $C_{55}H_{87}N_5O_{17}$ 1089.6; found ($M + H^+$) 1091.4.

*6.6.24. 4″-O-[Trans-β-(2-thienyl)acrylamido]carbamoyl-11-O-(4-methoxybenzyl)carbamoyl azithromycin (**28**)*

White solids, yield 71.5%, mp 142–144 °C, TLC Rf = 0.22 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3323, 2974, 2835, 1814, 1733, 1618, 1586, 1514, 1461, 1381, 1246, 1171, 1111, 1042 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.36–7.34 (m, 1H), 7.25–7.23 (m, 2H), 7.21–7.18 (m, 1H), 7.05–7.03 (m, 1H), 6.99–6.97 (m, 1H), 6.88–6.83 (m, 3H), 5.06–5.04 (m, 1H), 4.93 (s, 1H), 4.68–4.67 (m, 1H), 4.47–4.42 (m, 3H), 4.27–4.24 (m, 1H), 3.88–3.85 (m, 3H), 3.67–3.65 (m, 2H), 3.59–3.57 (m, 2H), 3.26–3.21 (m, 4H), 3.16–3.13 (m, 2H), 2.52–2.49 (m, 3H), 2.30–2.24 (m, 6H), 2.20 (s, 3H), 2.10–2.08 (m, 2H), 1.99 (s, 2H), 1.85–1.81 (m, 3H), 1.66–1.64 (m, 1H), 1.55–1.53 (m, 2H), 1.47–1.44 (m, 2H), 1.39–1.37 (m, 1H), 1.33–0.88 (m, 33H); MS (ESI) *m/z* calcd. for $C_{55}H_{87}N_5O_{16}S$ 1105.6; found ($M + H^+$) 1107.1.

*6.6.25. 4″-O-[Trans-β-(4-chlorophenyl)acrylamido]carbamoyl-11-O-(4-methoxybenzyl)carbamoyl azithromycin (**29**)*

White solids, yield 69.5%, mp 148–152 °C, TLC Rf = 0.24 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3319, 2937, 1813, 1732, 1634, 1590, 1514, 1461, 1380, 1172, 1092, 1040 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.66–7.63 (m, 1H), 7.41–7.33 (m, 5H), 7.27–7.25 (m, 2H), 7.24–7.23 (m, 2H), 5.02–5.00 (m, 1H), 4.93–4.92 (m, 1H), 4.65 (s, 1H), 4.43–4.34 (m, 3H), 4.24–4.22 (m, 1H), 3.84–3.82 (m, 3H), 3.67–3.65 (m, 2H), 3.57 (s, 2H), 3.29–3.21 (m, 4H), 3.17–3.15 (m, 2H), 2.55–2.50 (m, 3H), 2.29–2.23 (m, 6H), 2.19 (s, 3H), 2.12–2.10 (m, 2H), 2.01 (s, 2H), 1.89–1.82 (m, 3H), 1.68–1.66 (m, 1H), 1.58 (s, 2H), 1.49–1.47 (m, 2H), 1.40 (s, 1H), 1.33–0.88 (m, 33H); MS (ESI) *m/z* calcd. for $C_{57}H_{88}ClN_5O_{16}$ 1133.6; found ($M + H^+$) 1135.2.

*6.6.26. 4″-O-[Trans-β-(4-bromophenyl)acrylamido]carbamoyl-11-O-(4-methoxybenzyl)carbamoyl azithromycin (**30**)*

White solids, yield 72.1%, mp 149–152 °C, TLC Rf = 0.20 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3459, 2973, 2936, 1814, 1730, 1636, 1610, 1585, 1514, 1461, 1380, 1170, 1111, 1042 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.65–7.62 (m, 1H), 7.51–7.48 (m, 2H), 7.36–7.34 (m, 2H), 7.26–7.22 (m, 5H), 5.03–5.01 (m, 1H), 4.95 (s, 1H), 4.70–4.67 (m, 1H), 4.45–4.43 (m, 3H), 4.28–4.25 (m, 1H), 3.87–3.84 (m, 3H), 3.69–3.67 (m, 2H), 3.61–3.59 (m, 2H), 3.28–3.24 (m, 4H), 3.18–3.15 (m, 2H), 2.54–2.52 (m, 3H), 2.31–2.26 (m, 6H), 2.23 (s, 3H), 2.12–2.10 (m, 2H), 1.98 (s, 2H), 1.87–1.83 (m, 3H), 1.67–1.65 (m, 1H), 1.57–1.54 (m, 2H), 1.49–1.47 (m, 2H), 1.37–1.35 (m, 1H), 1.32–0.93 (m, 33H); MS (ESI) *m/z* calcd. for $C_{57}H_{88}BrN_5O_{16}$ 1177.5; found ($M + H^+$) 1180.9.

*6.6.27. 4″-O-[Trans-β-(4-nitrophenyl)acrylamido]carbamoyl-11-O-(4-methoxybenzyl)carbamoyl azithromycin (**31**)*

Light-yellow solids, yield 67.6%, mp 134–138 °C, TLC Rf = 0.20 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3341, 2974, 2938, 1731, 1635, 1612, 1517, 1461, 1382, 1345, 1172, 1111, 1039 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 8.20–8.18 (m, 1H), 7.76–7.71 (m, 1H), 7.66 (d, 1H, J = 7.8 Hz), 7.27–7.24 (m, 4H), 7.23 (d, 1H, J = 7.8 Hz), 6.89–6.87 (m, 2H), 5.05–5.03 (m, 1H), 4.96 (s, 1H), 4.73–4.71 (m, 1H), 4.50–4.47 (m, 3H), 4.31–4.28 (m, 1H), 3.89–3.86 (m, 3H), 3.72–3.70 (m, 2H), 3.59–3.57 (m, 2H), 3.27–3.23 (m, 4H), 3.19–3.17 (m, 2H), 2.55–2.51 (m, 3H), 2.32–2.24 (m, 6H), 2.20 (s, 3H), 2.15–2.13 (m, 2H), 1.97 (s, 2H), 1.85–1.82 (m, 3H), 1.69–1.67 (m, 1H), 1.59–1.56 (m, 2H), 1.50–1.48 (m, 2H), 1.39–1.38 (m, 1H), 1.29–0.79 (m, 33H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 176.68, 167.77, 164.46, 158.22, 148.47, 130.93, 129.83, 128.85, 128.63, 124.16, 113.95, 104.09, 96.49, 75.35, 73.93, 70.60, 65.58, 65.22, 55.29, 49.66, 45.65, 42.56, 40.31, 35.71, 35.10, 30.58, 29.75, 21.03, 19.18, 17.39, 14.34, 13.72, 11.48; MS (ESI) *m/z* calcd. for $C_{57}H_{88}N_6O_{18}$ 1144.6; found ($M + H^+$) 1146.1.

*6.6.28. 4″-O-[Trans-β-(2-methoxyphenyl)acrylamido]carbamoyl-11-O-(4-methoxybenzyl) carbamoyl azithromycin (**32**)*

White solids, yield 70.4%, mp 143–147 °C, TLC Rf = 0.22 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3463, 2973, 2836, 1815, 1732, 1614, 1514, 1462, 1381, 1171, 1110, 1046 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.97 (d, 1H, J = 15.6 Hz), 7.47 (d, 2H, J = 7.2 Hz), 7.36–7.33 (m, 2H), 7.24 (d, 2H, J = 7.2 Hz), 6.87–6.85 (m, 2H), 6.59 (d, 1H, J = 15.6 Hz), 5.07–5.05 (m, 1H), 4.99 (s, 1H), 4.76–4.74 (m, 1H), 4.55–4.52 (m, 3H), 4.33–4.30 (m, 1H), 3.87–3.85 (m, 6H), 3.71–3.69 (m, 2H), 3.57–3.55 (m, 2H), 3.28–3.25 (m, 4H), 3.21–3.18 (m, 2H), 2.53–2.49 (m, 3H), 2.31–2.25 (m, 6H), 2.18 (s, 3H), 2.14–2.11 (m, 2H), 2.03 (s, 2H), 1.87–1.85 (m, 3H), 1.71–1.68 (m, 1H), 1.57–1.55 (m, 2H), 1.52–1.50 (m, 2H), 1.41–1.39 (m, 1H), 1.36–0.86 (m, 33H); MS (ESI) *m/z* calcd. for $C_{58}H_{91}N_5O_{17}$ 1129.6; found ($M + H^+$) 1131.2.

*6.6.29. 4″-O-[Trans-β-(3,4-dimethoxyphenyl)acrylamido] carbamoyl-11-O-(4-methoxybenzyl) carbamoyl azithromycin (**33**)*

White solids, yield 66.2%, mp 142–146 °C, TLC Rf = 0.25 ($CH_2Cl_2$:MeOH = 5:1); IR (KBr): 3501, 2974, 2836, 1813, 1733, 1630, 1514, 1463, 1381, 1168, 1110, 1040 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$): 7.65–7.63 (m, 1H), 7.22–7.16 (m, 3H), 7.07–7.05 (m, 1H), 6.88–6.83 (m, 4H), 5.08–5.05 (m, 1H), 4.96 (s, 1H), 4.73–4.71 (m, 1H), 4.52–4.48 (m, 3H), 4.32–4.31 (m, 1H), 3.83–3.81 (m, 9H), 3.70–3.68 (m, 2H), 3.55–3.53 (m, 2H), 3.30–3.27 (m, 4H), 3.22–3.20 (m, 2H), 2.54–2.52 (m, 3H), 2.32–2.26 (m, 6H), 2.20–2.18 (m, 3H), 2.13–2.09 (m, 2H), 2.01–1.99 (m, 2H), 1.85–1.83 (m, 3H), 1.71–1.69 (m, 1H), 1.58–1.56 (m, 2H), 1.53–1.51 (m, 2H), 1.42–1.40 (m, 1H), 1.43–0.94 (m, 33H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 176.65, 165.58, 158.18, 151.22, 149.27, 130.97, 130.28, 129.83, 129.37, 129.29, 127.36, 122.38, 113.93, 111.09, 109.90, 75.26, 73.82, 73.19, 70.66, 69.02, 65.23, 63.31, 61.96, 55.97, 55.90, 55.28, 49.68, 45.55, 43.07, 42.56, 40.35, 35.12, 29.71, 29.25, 27.54, 21.76, 21.30, 21.02, 17.33, 14.35, 11.48; MS (ESI) *m/z* calcd. for $C_{59}H_{93}N_5O_{18}$ 1159.7; found ($M + H^+$) 1161.3.

## Acknowledgments

This research was supported financially by the National Natural Science Foundation of China (21072114), the Natural Science Foundation of Shandong (ZR2015BM019), and China–Australia

Centre for Health Sciences Research (CACHSR, 2014GJ06).

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.09.020.

## References

[1] S. Pal, A journey across the sequential development of macrolides and ketolides related to erythromycin, Tetrahedron 62 (2006) 3171–3200.
[2] L. Zhang, B. Jiao, X. Yang, L. Liu, S. Ma, Synthesis and antibacterial activity of new 4"-O-carbamates of 11,12-cyclic carbonate erythromycin A 6,9-imino ether, J. Antibiot. 64 (2011) 243–247.
[3] S. Djokic, G. Kobrehel, G. Lazarevski, Antibacterial in vitro evaluation of 10-dihydro-10-deoxo-11-azaerythromycin A: synthesis and structure-activity relationship of its acyl derivatives, J. Antibiot. 40 (1987) 1006–1015.
[4] G.M. Bright, A.A. Nagel, J. Bordner, K.A. Desai, J.N. Dibrino, J. Nowakowska, L. Vincent, R.M. Watrous, F.C. Sciavolino, A.R. English, Synthesis, in vitro and in vivo activity of novel 9-deoxo-9a-AZA-9a-homoerythromycin A derivatives; a new class of macrolide antibiotics, the azalides, J. Antibiot. 41 (1988) 1029–1047.
[5] S. Morimoto, Y. Takahashi, Y. Watanabe, S. Omura, Chemical modification of erythromycins. I. Synthesis and antibacterial activity of 6-O-methylerythromycins A, J. Antibiot. 37 (1984) 187–189.
[6] Y. Watanabe, T. Adachi, T. Asaka, M. Kashimura, T. Matsunaga, S. Morimoto, Chemical modification of erythromycins. XII. A facile synthesis of clarithromycin (6-O-methylerythromycin A) via 2′-silylethers of erythromycin A derivatives, J. Antibiot. 46 (1993) 1163–1167.
[7] L. Zhang, S. Linchen, L. Zhaopeng, H. Li, Y. Lu, Z. Li, S. Ma, Synthesis and antibacterial activity of novel 3-O-carbamoyl derivatives of clarithromycin and 11,12-cyclic carbonate azithromycin, Eur. J. Med. Chem. 45 (2010) 915–922.
[8] S. Ma, R. Ma, Z. Liu, C. Ma, X. Shen, 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, Eur. J. Med. Chem. 44 (2009) 4010–4020.
[9] A. Harimaya, S. Yokota, K. Sato, N. Yamazaki, T. Himi, N. Fujii, High prevalence of erythromycin resistance and macrolide-resistance genes, *mefA* and *ermB*, in *Streptococcus pneumoniae* isolates from the upper respiratory tracts of children in the Sapporo district, Japan, J. Infect. Chemother. 13 (2007) 219–223.
[10] S. Ma, B. Jiao, Z. Liu, H. Wang, R. Xian, M. Zheng, H. Lou, Synthesis and antibacterial activity of 4″, 11-di-O-arylalkylcarbamoyl azithromycin derivatives, Bioorg. Med. Chem. Lett. 19 (2009) 1698–1701.
[11] J.H. Jorgensen, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically: Approved Standard: NCCLS Document M7–A3 [M], NCCLS, 1993.
[12] X. Lin, S. Ma, M. Yan, Y. Wang, S. Ma, Synthesis and antibacterial evaluation of novel 11,4″-disubstituted azithromycin analogs with greatly improved activity against erythromycin-resistant bacteria, Eur. J. Med. Chem. 59 (2013) 209–217.