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ORIGINAL ARTICLE

Novel azithromycin derivatives with the C-4″ bisamide side chains: synthesis and biological evaluation against gram-positive bacteria

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Novel azithromycin (AZM) derivatives with the C-4″ bisamide side chains were synthesized and evaluated for their *in vitro* antibacterial activities. The 4″-*O*-(benzamido)alkyl carbamates showed excellent activity against the erythromycin-susceptible *Streptococcus pneumoniae* and exhibited greatly improved activity against erythromycin-resistant *S. pneumoniae*. Among them, compounds 5g and 6g, which had the same electron-withdrawing group, 3,5-dinitrophenyl, on the termination of their C-4″ bisamide side chains, demonstrated the most potent activity against erythromycin-resistant *S. pneumoniae* expressing the *erm* gene, the *mef* gene and the *erm* and *mef* genes, showing 128-fold, 33-fold and 32-fold improved activity in comparison with the parent AZM.
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INTRODUCTION

Macrolide antibiotics have been commonly used effectively and safely for the treatment of respiratory tract infections since the first macrolide erythromycin A was used clinically in the early 1950's. However, intensive emergence of the resistance to various antimicrobials is a pandemic phenomenon, which severely threatens therapeutic effectiveness of the macrolides as well.[1] To overcome the resistance of bacteria to the macrolides, the structural modifications of existing macrolide antibiotics such as clarithromycin[2] and azithromycin[3] (AZM) have been carried out, leading to the discovery of third-generation macrolides known as ketolides. Telithromycin, a typical example of ketolides, which is well known for excellent activity against resistant strains and lower inductivity of the *erm* gene encoding resistance, has been launched in the market.[4–6] It has been reported that the C-11,12 prolonged carbamate side chain of telithromycin can interact with a secondary ribosomal binding site A752 directly in domain II of the 23S rRNA in addition to the main interaction with A2058 in domain V, resulting in tighter binding to bacterial ribosomes and improved activity against *erm*-resistant organisms.[7] Another promising ketolide, cethromycin,[8] which can also interact with A752 through its C-6 prolonged side chain, is in last-stage development at present. Unfortunately, severe hepatotoxicity suppressing the clinical use of telithromycin has been reported. Great efforts to develop new generation macrolides with low toxicity and potent activity have led to the discovery of the C-4″ modified macrolides such as CP-544372[9] and A-66332.[10] CP-544372, which contains a long C-4″ anchor group with six atoms from the 4″-oxygen atom to the terminal aromatic ring, exhibits excellent *in vitro* and *in vivo* activity against macrolide-resistant strains encoded by the *erm* gene.[11] It has been revealed that the side chains of CP-544 372 can reach the chloramphenicol-binding sites in the peptidyl transferase center region[9] and impart a higher affinity to the resistant ribosomes.

To explore the contribution of length of the C-4″ side chains to the antibacterial activity, several series of novel 4″-*O*-carbamate derivatives of AZM, characterized by novel C-4″ arylalkyl groups with three, four, eight and nine atoms from the 4″-oxygen atom to the terminal aromatic ring, were designed, synthesized and evaluated in our research group. The 4″-*O*-carbamates containing short side chains with three or four atoms from the 4″-oxygen atom to the terminal aromatic ring not only retained the activity against susceptible *Streptococcus pneumoniae*, but also showed improved activity against resistant *S. pneumoniae* encoded by the *erm* gene, and the *erm* and *mef* genes in comparison with macrolide erythromycin A, clarithromycin and AZM.[12] Especially, the 4″-*O*-carbamates with long side chains, the lengths of which are eight or nine atoms from the 4″-oxygen atom to the terminal aromatic ring, showed more remarkably improved activity against the resistant strains encoded by the *erm* gene, and the *erm* and the *mef* genes than the above references and the 4″-*O*-carbamates with short side chains, which suggested that the 4″-*O*-carbamates with long side chains could have good activity against the resistant strains.[13] On the basis of the above results, two series of novel AZM derivatives with the C-4″ bisamide side chains

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containing six or eight atoms from the 4″-oxygen atom to the terminal aromatic ring were designed, synthesized and evaluated for their *in vitro* antibacterial activities in this paper. The introduced C-4″ bisamide side chains were expected to interact with the new binding sites in the peptidyl transferase center region[14] and produce an additional affinity for the resistant ribosome through hydrogen bonding, π-stacking and electrostatic interactions.[13]

RESULTS

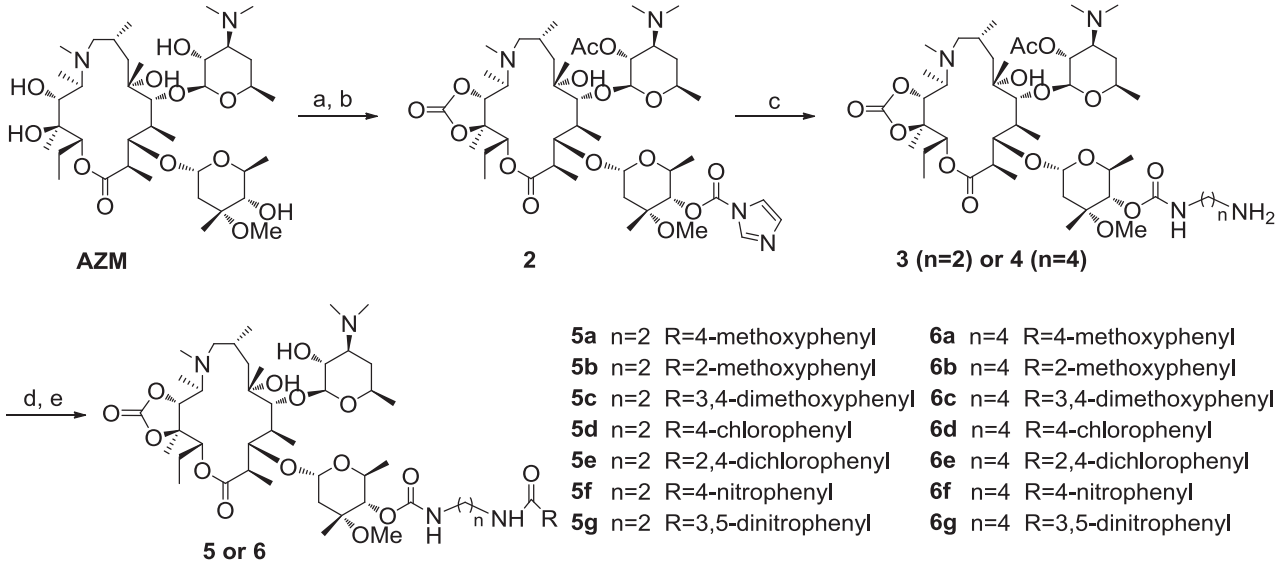
Chemistry

The synthesis of 4″-*O*-(benzamido)alkyl carbamates of 11,12-cyclic carbonate AZM **5a–g** and **6a–g** started from the commercially available AZM (Scheme 1). 2′-*O*-acetylation of AZM with acetic anhydride (Ac_2O) was followed by introduction of C-4″ acylimidazole group and 11,12-cyclic carbonate group utilizing 1,1′-carbonyldiimidazole in the presence of triethylamine to generate 4″-*O*-acylimidazolide (**2**). The reaction of **2** with ethylenediamine or 1,4-butanediamine hydrochloride catalyzed by 1,8-diazabicyclo(5.4.0)undec-7-ene provided 4″-*O*-(2-aminoethyl)carbamate (**3**) or 4″-*O*-(4-aminobutyl)carbamate (**4**), respectively. Finally, 4″-*O*-(benzamido)ethyl carbamates of 11,12-cyclic carbonate AZM (**5a–g**) and 4″-*O*-(benzamido)butyl carbamates of 11,12-cyclic carbonate AZM (**6a–g**) were obtained by the condensation of **3** or **4** with the corresponding substituted benzoic acid in the presence of 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole, and the subsequent 2′-*O*-deacetylation at 55 °C in methanol in yields ranging from 75.8 to 87.6%.

Antibacterial activity

The *in vitro* activities of the 4″-*O*-(benzamido)alkyl carbamates **5a–g** and **6a–g**, as well as macrolide erythromycin A, clarithromycin and AZM as references, were evaluated by using broth microdilution method as shown in Table 1. *S. pneumoniae* ATCC49619 is an erythromycin-susceptible strain, and *S. pneumoniae* B1, *S. pneumoniae* A22072 and *S. pneumoniae* AB11 are three erythromycin-resistant strains whose resistance were encoded by the *erm* gene, the *mef* gene, and the *erm* and *mef* genes, respectively. *Staphylococcus aureus* ATCC25923 is an erythromycin-susceptible strain. *S. aureus* and *S. aureus* ATCC29213 are penicillin-resistant and methicillin-resistant strains, respectively.

MIC values for 4″-*O*-(benzamido)alkyl carbamates of 11,12-cyclic carbonate AZM **5a–g** and **6a–g** are presented in Table 1. Most of the 4″-*O*-(benzamido)alkyl carbamates showed excellent activity (0.5–0.12 μg ml^{-1}) against the erythromycin-susceptible *S. pneumoniae* ATCC49619. Among them, compounds **5g**, **6f** and **6g**, which had the electron-withdrawing groups on the termination of their C-4″ bisamide side chains, were found to have the most potent activity (0.12 μg ml^{-1}), but weaker than the parent AZM. In particular, the most active compounds **5g** and **6g** possessed the same terminal group, 3,5-dinitrophenyl, on their C-4″ bisamide side chains, but the side chain of the former was two atoms less than that of the latter. As for the activity against three erythromycin-resistant *S. pneumoniae* strains, all of the 4″-*O*-(benzamido)ethyl carbamates **5a–g** exhibited improved activity against erythromycin-resistant *S. pneumoniae* expressing the *erm* gene, and the *erm* and *mef* genes, showing 4–128-fold and 4–32-fold better activity than the parent AZM, respectively. Among them, compounds **5f** and **5g** showed potent activity (0.5–0.12 μg ml^{-1}) against erythromycin-resistant *S. pneumoniae* A22072 expressing the *mef* gene. Especially, compound **5g** presented the most potent activity (1 and 0.12 μg ml^{-1}) against erythromycin-resistant *S. pneumoniae* strains expressing the *erm* gene or the *mef* gene, exhibiting 128-fold and 33-fold better activity than the parent AZM. On the other hand, all of the 4″-*O*-(benzamido)butyl carbamates **6a–g** had improved activity against erythromycin-resistant *S. pneumoniae* expressing the *erm* gene, the *mef* gene, and the *erm* and *mef* genes, exhibiting 4–128-fold, 4–32-fold and 8–32-fold higher activity than the parent AZM, respectively. Among them, compounds **6a**, **6b**, **6f** and **6g** displayed significantly potent activity (0.5–0.12 μg ml^{-1}) against erythromycin-resistant *S. pneumoniae* A22072 expressing the *mef* gene, and compound **6g** showed potent activity (1 μg ml^{-1}) against *S. pneumoniae* B1 expressing the *erm* gene. In particular, compound **6g** possessed the highest activity against erythromycin-resistant *S. pneumoniae* expressing both the *erm* gene and the *mef* gene, comparable to compound **5g**.



Scheme 1 Reagents and conditions: (a) Ac_2O, CH_2Cl_2, Et_3N, room temperature, 12 h, 96%; (b) 1,1′-carbonyldiimidazole, toluene, 55 °C, 48 h, 87%; (c) Ethylenediamine or 1,4-butanediamine hydrochloride, 1,8-diazabicyclo(5.4.0)undec-7-ene, Et_3N, room temperature, 4 h, 93%; (d) R-COOH, 1,3-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole, tetrahydrofuran, 0 °C, 0.5–1 h; room temperature, 2 h, 86–90%; (e) CH_3OH, 55 °C, 24 h, 76–88%.

Table 1 ***In vitro*** **antibacterial activity of 4″-*O*-(benzamido)alkyl carbamates of 11,12-cyclic carbonate azithromycin**

	Strain/MIC($\mu g\ ml^{-1}$)						
Compound	*S. pneumoniae ATCC49619*[a]	*S. pneumoniae B1*[b]	*S. pneumoniae A22072*[c]	*S. pneumoniae AB11*[d]	*S. aureus ATCC25923*[e]	*S. aureus*[f]	*S. aureus ATCC29213*[g]
5a	4	32	4	64	4	4	16
5b	0.5	32	8	64	4	64	8
5c	2	32	4	64	4	8	32
5d	0.5	8	1	32	4	2	16
5e	0.5	16	2	64	4	4	8
5f	0.5	4	0.5	64	4	1	16
5g	0.12	1	0.12	8	16	1	8
6a	1	4	0.25	16	4	1	32
6b	2	4	0.5	16	4	32	16
6c	2	32	1	32	8	16	64
6d	0.5	8	1	16	4	64	8
6e	1	4	1	16	2	64	16
6f	0.12	2	0.5	16	4	32	4
6g	0.12	1	0.12	8	2	16	4
EAM	0.03	128	8	256	0.06	0.25	0.12
CAM	0.03	64	4	128	0.12	0.03	0.25
AZM	0.03	128	4	256	0.25	0.12	1

Abbreviations: AZM, azithromycin; CAM, clarithromycin; EAM, macrolide erythromycin A.
[a]*S. pneumoniae* ATCC49619: erythromycin-susceptible strain.
[b]*S. pneumoniae* B1: erythromycin-resistant strain encoded by the *erm* gene.
[c]*S. pneumoniae* A22072: erythromycin-resistant strain encoded by the *mef* gene.
[d]*S. pneumoniae* AB11: erythromycin-resistant strain encoded by the *erm* and *mef* genes.
[e]*S. aureus* ATCC25923: erythromycin-susceptible strain.
[f]*S. aureus*: penicillin-resistant strain isolated clinically, not characterized.
[g]*S. aureus* ATCC29213: methicillin-resistant strain.

Although the most active compounds **5g** and **6g** possessed different length of the C-4″ bisamide side chain, they had the same electron-withdrawing group, 3,5-dinitrophenyl, on the termination of C-4″ bisamide side chain.

DISCUSSION

On the whole, the series of 4″-*O*-(benzamido)butyl carbamates with eight atoms from the 4″-oxygen atom to the terminal benzene ring on the C-4″ bisamide side chains showed more greatly improved activity against the erythromycin-resistant *S. pneumoniae* than the series of 4″-*O*-(benzamido)ethyl carbamates with six atoms from the 4″-oxygen atom to the terminal benzene ring. In addition, the compounds with the electron-withdrawing groups showed higher activity against the tested erythromycin-resistant *S. pneumoniae* than those with the electron donating groups in the series of 4″-*O*-(benzamido)ethyl carbamates. The results described above indicated that the C-4″ elongated bisamide side chain with eight atoms between the 4″-oxygen atom and the terminal aromatic ring might be a suitable length, and the terminal 3,5-dinitrophenyl group might easily interact with the new binding sites of nucleotides in the peptidyl transferase center region through hydrogen bonding, π-stacking etc., resulting in a higher affinity for the ribosome of resistant bacteria.

In contrast to the greatly improved activity against the erythromycin-resistant *S. pneumoniae* strains, the 4″-*O*-(benzamido)alkyl carbamates **5a–g** and **6a–g** lost activity against the erythromycin-susceptible and resistant *S. aureus* strains compared with the parent AZM. This result led us to presume that the long C-4″ bisamide side chains on the 4″-*O*-(benzamido)alkyl carbamates could not interact with the secondary ribosomal binding sites in the peptidyl transferase center region, and further block the interaction of the 4″-*O*-(benzamido)alkyl carbamates with the main binding site A2058 in ribosomes of *S. aureus* as well.

In summary, novel 4″-*O*-((benzamido)alkyl carbamates of 11,12-cyclic carbonate AZM were designed, synthesized and evaluated for their *in vitro* antibacterial activities. Most of the 4″-*O*-(benzamido)alkyl carbamates showed excellent activity against the erythromycin-susceptible *S. pneumoniae* and some of them exhibited greatly improved activity against erythromycin-resistant *S. pneumoniae* expressing the *erm* gene, the *mef* gene, and the *erm* and *mef* genes. Among them, compounds **5g** and **6g**, which had the same electron-withdrawing group, 3,5-dinitrophenyl, on the termination of their C-4″ bisamide side chains, demonstrated the most potent activity against the erythromycin-susceptible and erythromycin-resistant *S. pneumoniae*. It is noteworthy that the series of 4″-*O*-(benzamido)butyl carbamates with eight atoms from the 4″-oxygen atom to the terminal benzene ring on the C-4″ bisamide side chains showed more greatly improved activity against the erythromycin-resistant *S. pneumoniae* than the series of 4″-*O*-(benzamido)ethyl carbamates with six atoms from the 4″-oxygen atom to the terminal benzene ring.

METHODS

General experimental procedures

All necessary solvents were purified before 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). TLC was detected by UV detector at 254 nm and sulfuric acid color reaction. 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). IR spectra were recorded on KBr pellets using Nicolet Nexus 470FT–IR spectrometer (Nicolet, Madison, WI,

USA). ^{1}H NMR spectra were recorded on a Bruker Avance DRX 600 spectrometer (Bruker, Fällanden, Switzerland) at ambient temperature with tetramethylsilane as an internal standard. Mass spectra were recorded on an API 4000 instrument (Applied Biosystems, Foster City, CA, USA) and the high-resolution mass spectra data were obtained using Agilent Q-TOF6510 mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). UV spectra were obtained on Shimadzu UV-2550 spectrometer (Shimadzu, Tokyo, Japan). The m.p. are uncorrected and were determined on an X–6 melting point apparatus (Beijing Tianchengwode Biotech Co. Ltd, Beijing, China). AZM that was used as starting material was obtained from Nexchem Pharmaceutical Co., Ltd (Jinhuacity, Zhejiang, China).

2′-*O*-acetyl-4″-*O*-acylimidazolyl AZM-11,12-carbonate (2)

To a solution of AZM (2.0 g, 2.67 mmol) in dichloromethane (20 ml) at room temperature was added Ac_2O (0.7 ml, 7.38 mmol) and Et_3N (3.00 ml, 21.65 mmol). The resulting solution was allowed to stir for 12 h at room temperature. The reaction was quenched with 5% aqueous $NaHCO_3$ (20 ml) and the aqueous layer was extracted with dichloromethane (3×10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford 2.02 g (95.6%) of acetate product as a white solid: m.p. 167–170 °C, R_f=0.52 (dichloromethane/methanol, 10:1); MS (ESI) m/z calculated for $C_{40}H_{75}N_2O_{13}$ 791.5269; found ($M+H^+$) 791.5278.

To a solution of the acetate product (1.5 g, 1.90 mmol) in toluene (20 ml) was added Et_3N (0.60 ml, 4.33 mmol) and 1,1′-carbonyldiimidazole (1.34 g, 7.60 mmol). The resulting solution was stirred at 55 °C for 48 h. The reaction was concentrated in vacuo and the residue was dissolved with dichloromethane (20 ml), which 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 vacuo. The residue was purified by flash chromatography (dichloromethane/methanol, 20:1) to afford 1.50 g (86.6%) of **2** as a white solid: m.p. 117–120 °C; R_f=0.61 (dichloromethane/methanol, 10:1). MS (ESI) m/z calculated for $C_{45}H_{75}N_4O_{15}$ 911.5229; found ($M+H^+$) 911.5219.

2′-*O*-acetyl-4″-*O*-aminoalkyl carbamoyl AZM 11,12-carbonate (3) or (4)

To a solution of **2** (1.5 g, 1.65 mmol) in DMF (15 ml) was added 1,8-diazabicyclo(5.4.0)undec-7-ene (0.33 ml, 2.25 mmol) and ethylenediamine (3.3 mmol) or 1,4-butanediamine hydrochloride (3.3 mmol). The resulting solution was stirred for 4 h at room temperature. The reaction was quenched with 5% aqueous $NaHCO_3$ (20 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 of 4″-*O*-(2-aminoethyl)carbamate **3** or 4″-*O*-(4-aminobutyl)carbamate **4** in yield of about 93.2%.

General methods for 4″-*O*-(benzamido)alkyl carbamates of 11,12-cyclic carbonate AZM (5a–g or 6a–g)

The solution of the corresponding substituted benzoic acid (1 eq.) and 1-hydroxybenzotriazole (1.1 eq.) in tetrahydrofuran (15 ml) was added 1,3-dicyclohexylcarbodiimide (1.1 eq.) at 0 °C and stirred for 0.5–1 h at the same temperature. Then the 4″-*O*-aminoalkyl carbamates **3** (or **4**) was added, the resulting solution was stirred for another 2 h at room temperature.

The reaction was concentrated in vacuo and ethyl acetate (15 ml) was added. After stirring for 1 h, the insoluble substance was filtered out. The filtrate was quenched with 5% aqueous $NaHCO_3$ (20 ml) and the aqueous layer was extracted with ethyl acetate (2×15 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford a crude product in 85.7–90.2% yield.

A solution of the above crude product in methanol (15 ml) was heated to 55 °C and stirred for 12 h at the same temperature. After concentrating the reaction solution in vacuo, the residue was purified by flash chromatography (dichloromethane/methanol, 30:1) to give the desired products **5a–g** (or **6a–g**) in yields ranging from 75.8 to 87.6%.

4″-*O*-(((4-Methoxybenzamido)ethyl)carbamoyl) AZM-11,12-carbonate (5a)

White solid, yield 82.9%, m.p. 158–161 °C, TLC R_f=0.36 (methanol/dichloromethane, 1:10); IR (KBr): 3416, 2973, 2937, 2880, 2830, 2788, 1813, 1727, 1654, 1613, 1534, 1505, 1457, 1379, 1353, 1334, 1302, 1276, 1256, 1235, 1166, 1110, 1073, 1046 and 1015 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.77 (d, 2H, *J*=8.4 Hz), 6.90 (d, 2H, *J*=9.0 Hz), 5.01 (d, 1H, *J*=4.2 Hz), 4.88 (dd, 1H, *J*=9.6 Hz, *J*=6.6 Hz), 4.56–4.46 (m, 2H), 4.36–4.24 (m, 2H), 3.85 (s, 3H), 3.70–3.64 (m, 1H), 3.64–3.52 (m, 3H), 3.52–3.42 (m, 2H), 3.40–3.32 (m, 2H), 3.27 (s, 3H), 2.88–2.78 (m, 2H), 2.59 (s, 6H), 2.44–2.40 (m, 2H), 2.36–2.30 (m, 2H), 2.20 (s, 3H), 2.30–2.20 (m, 1H), 1.94–1.88 (m, 1H), 1.86–1.78 (m, 2H), 1.66–1.50 (m, 2H), 1.44 (s, 3H), 1.38–1.24 (m, 6H), 1.22–1.16 (m, 6H), 1.14–1.10 (m, 3H), 1.10–1.04 (m, 6H), 1.02–0.98 (m, 3H) and 0.96–0.88 (m, 6H); HRMS (ESI) m/z calculated for $C_{50}H_{83}N_4O_{16}$ ($M+H^+$) 995.5804, found 995.5810.

4″-*O*-(((2-Methoxybenzamido)ethyl)carbamoyl) AZM-11,12-carbonate (5b)

White solid, yield 85.3%, m.p. 160–162 °C, TLC R_f=0.40 (methanol/dichloromethane, 1:10); IR (KBr): 3400, 3075, 2972, 2936, 2880, 1812, 1721, 1648, 1600, 1532, 1484, 1463, 1383, 1336, 1301, 1238, 1166, 1108, 1085, 1045 and 1015 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.80 (d, 1H, *J*=7.8 Hz), 7.61 (d, 1H, *J*=7.8 Hz), 7.43 (t, 1H, *J*=7.8 Hz), 7.04 (t, 1H, *J*=7.8 Hz), 5.01 (d, 1H, *J*=4.2 Hz), 4.86 (dd, 1H, *J*=9.0 Hz, *J*=6.0 Hz), 4.58–4.48 (m, 2H), 4.34–4.22 (m, 2H), 3.96 (s, 3H), 3.78–3.70 (m, 1H), 3.66–3.54 (m, 3H), 3.54–3.42 (m, 4H), 3.30 (s, 3H), 2.88–2.70 (m, 9H), 2.46–2.40 (d, 1H, *J*=10.2 Hz), 2.36–2.30 (d, 1H, *J*=9.0 Hz), 2.24–2.10 (m, 5H), 2.04–2.00 (m, 1H), 1.90–1.80 (m, 2H), 1.62–1.58 (m, 5HH), 1.46–1.40 (m, 2H), 1.28–1.22 (m, 7H), 1.22–1.14 (m, 6H), 1.14–1.10 (m, 3H), 1.10–1.02 (m, 3H), 1.02–0.96 (m, 3H), 0.96–0.84 (m, 6H); HRMS (ESI) m/z calculated for $C_{50}H_{83}N_4O_{16}$ ($M+H^+$) 995.5804, found 995.5779.

4″-*O*-(((3,4-dimethoxybenzamido)ethyl)carbamoyl) AZM-11,12-carbonate (5c)

White solid, yield 83.7%, m.p. 159–162 °C, TLC R_f=0.37 (methanol/dichloromethane, 1:10); IR (KBr): 3411, 3083, 2972, 2937, 2879, 2836, 1812, 1726, 1647, 1604, 1584, 1507, 1459, 1383, 1353, 1311, 1269, 1232, 1166, 1110, 1074, 1045 and 1016 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.45 (d, 1H, *J*=1.8 Hz), 7.32 (dd, 1H, *J*=8.4 Hz, *J*=6.6 Hz), 7.04–6.98 (m, 1H), 5.07 (d, 1H, *J*=4.8 Hz), 4.88 (dd, 1H, *J*=9.6 Hz, *J*=6.6 Hz), 4.53 (d, 1H, *J*=9.6 Hz) 4.46–4.30 (m, 3H), 3.96–3.90 (m, 6H), 3.70–3.60 (m, 3H), 3.60–3.44 (m, 5H), 3.28 (s, 3H), 2.90–2.82 (m, 2H), 2.74–2.64 (m, 1H), 2.46–2.30 (m, 8H), 2.24–2.16 (m, 4H), 2.08–2.02 (m, 2H), 1.88–1.74 (m, 2H), 1.64–1.58 (m, 3H), 1.48–1.38 (m, 4H), 1.30–1.22 (m, 6H), 1.22–1.12 (m, 7H), 1.12–1.00 (m, 9H) and 0.96–0.86 (m, 6H); HRMS (ESI) m/z calculated for $C_{51}H_{85}N_4O_{17}$ ($M+H^+$) 1025.5910, found 1025.5896.

4″-*O*-(((4-chlorobenzamido)ethyl)carbamoyl) AZM-11,12-carbonate (5d)

White solid, yield 87.6%, m.p. 163–165 °C, TLC R_f=0.36 (methanol/dichloromethane, 1:10); IR (KBr): 3384, 3068, 2973, 2937, 2879, 1812, 1726, 1656, 1596, 1532, 1486, 1459, 1382, 1353, 1335, 1314, 1256, 1236, 1167, 1110, 1074, 1045 and 1014 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.79 (d, 2H, *J*=8.4 Hz), 7.39 (d, 2H, *J*=7.8 Hz), 5.05 (d, 1H, *J*=4.8 Hz), 4.90 (dd, 1H, *J*=9.6 Hz, *J*=6.6 Hz), 4.54 (d, 1H, *J*=9.6 Hz), 4.49 (d, 1H, *J*=7.2 Hz), 4.36–4.26 (m, 2H), 3.70–3.52 (m, 4H), 3.52–3.44 (m, 3H), 3.38–3.36 (m, 1H), 3.17 (s, 3H), 2.88–2.78 (m, 2H), 2.62–2.50 (m, 7H), 2.46–2.40 (m, 1H), 2.36–2.30 (m, 1H), 2.22 (s, 3H), 2.04–2.00 (m, 1H), 1.94–1.88 (m, 1H), 1.86–1.78 (m, 2H), 1.64–1.52 (m, 3H), 1.44 (s, 3H), 1.42–1.24 (m, 7H), 1.22–1.16 (m, 6H), 1.14–1.10 (m, 3H), 1.10–1.04 (m, 6H), 1.04–0.98 (m, 3H) and 0.96–0.88 (m, 6H); HRMS (ESI) m/z calculated for $C_{49}H_{80}ClN_4O_{15}$($M+H^+$) 999.5309, found 999.5277.

4″-*O*-(((2,4-dichlorobenzamido)ethyl)carbamoyl) AZM-11,12-carbonate (5e)

White solid, yield 80.2%, m.p. 165–168 °C, TLC R_f=0.37 (methanol/dichloromethane, 1:10); IR (KBr): 3431, 3088, 2971, 2933, 1814, 1728, 1664, 1589, 1518,

1459, 1379, 1353, 1334, 1301, 1235, 1166, 1108, 1087, 1073, 1045 and 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.58 (d, 1H, *J*=8.4 Hz), 7.41 (d, 1H, *J*=1.8 Hz), 7.30 (dd, 1H, *J*=8.4 Hz, *J*=6.6 Hz), 5.07 (d, 1H, *J*=4.2 Hz), 4.88 (dd, 1H, *J*=9.0 Hz, *J*=6.0 Hz), 4.52 (d, 1H, *J*=10.2 Hz), 4.46–4.30 (m, 3H), 3.70–3.60 (m, 2H), 3.60–3.54 (m, 3H), 3.52–3.42 (m, 3H), 3.32 (s, 3H), 2.92–2.80 (m, 2H), 2.62–2.58 (m, 1H), 2.42–2.40 (m, 1H), 2.38–2.26 (m, 7H), 2.22–2.16 (s, 4H), 2.08–2.02 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.66 (m, 4H), 1.64–1.54 (m, 2H), 1.44 (s, 3H), 1.32–1.22 (m, 7H), 1.22–1.16 (m, 6H), 1.12–1.08 (m, 3H), 1.08–1.00 (m, 3H) and 0.96–0.80 (m, 9H); HRMS (ESI) m/z calculated for $C_{49}H_{79}Cl_2N_4O_{15}$ ($M+H^+$) 1033.4919, found 1033.4889.

4″-*O*-(((4-nitrobenzamido)ethyl)carbamoyl) AZM-11,12-carbonate (5f)

White solid, yield 85.7%, m.p. 130–132 °C, TLC R_f=0.39 (methanol/dichlormethane, 1:10); IR (KBr): 3397, 3070, 2973, 2937, 2880, 1812, 1727, 1665, 1601, 1527, 1488, 1459, 1382, 1348, 1300, 1256, 1236, 1167, 1109, 1074, 1045 and 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 8.27 (dd, 2H, *J*=9.0 Hz, *J*=6.6 Hz), 8.07 (d, 2H, *J*=8.4 Hz), 5.05 (d, 1H, *J*=4.2 Hz), 4.90 (dd, 1H, *J*=9.0 Hz, *J*=6.0 Hz), 4.58–4.50 (m, 1H), 4.42–4.38 (s, 1H), 4.34–4.26 (m, 2H), 3.74–3.58 (m, 4H), 3.58–3.44 (m, 4H), 3.44–3.38 (m, 2H), 3.27 (s, 3H), 2.86–2.74 (m, 3H), 2.60–2.54 (s, 7H), 2.46–2.42 (m, 1H), 2.36–2.28 (m, 2H), 2.21 (s, 3H), 2.18–2.08 (m, 2H), 2.08–1.90 (m, 3H), 1.86–1.78 (m, 2H), 1.54–1.66 (m, 2H), 1.44 (s, 3H,), 1.38–1.30 (m, 1H), 1.27 (s, 3H), 1.22–1.16 (m, 2H), 1.16–1.12 (m, 3H), 1.10–1.04 (m, 6H), 1.04–0.98 (m, 3H) and 0.96–0.88 (m, 6H); HRMS (ESI) m/z calculated for $C_{49}H_{80}N_5O_{17}$($M+H^+$) 1010.5549, found 1010.5528.

4″-*O*-(((3,5-dinitrobenzamido)ethyl)carbamoyl) AZM-11,12-carbonate (5g)

Slightly yellow solid, yield 75.8%, m.p. 129–131 °C, TLC R_f=0.30 (methanol/dichlormethane, 1:10); IR (KBr): 3431, 3104, 2973, 2937, 2880, 1812, 1729, 1672, 1629, 1544, 1458, 1382, 1344, 1304, 1258, 1236, 1167, 1111, 1074, 1045 and 10145 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 9.15 (t, 1H, *J*=7.8 Hz), 9.05 (d, 1H, *J*=1.2 Hz), 7.30 (dd, 1H, *J*=8.4 Hz, *J*=6.6 Hz), 5.09 (d, 1H, *J*=4.8 Hz), 4.89 (dd, 1H, *J*=9.6 Hz, *J*=6.6 Hz), 4.61 (d, 1H, *J*=9.6 Hz), 4.46–4.34 (m, 3H), 3.70–3.64 (m, 2H), 3.64–3.46 (m, 5H), 3.30 (s, 4H), 2.94–2.88 (m, 1H), 2.88–2.80 (m, 1H), 2.70–2.60 (s, 1H), 2.40–2.43 (m, 8H), 2.19 (s, 3H), 2.08–2.02 (m, 1H), 1.84–1.74 (m, 2H), 1.70–1.62 (m, 2H), 1.62–1.50 (m, 2H), 1.44 (s, 3H), 1.30–1.20 (m, 7H), 1.22–1.16 (m, 6H), 1.12–1.08 (m, 3H), 1.10–1.02 (m, 5H) and 0.96–0.82 (m, 9H); HRMS (ESI) m/z calculated for $C_{49}H_{79}N_6O_{19}$($M+H^+$) 1055.5400, found 1055.5387.

4″-*O*-(((4-methoxybenzamido)butyl)carbamoyl) AZM-11,12-carbonate (6a)

White solid, yield 86.8%, m.p. 163–166 °C, TLC R_f=0.35 (methanol/dichlormethane, 1:10); IR (KBr): 3419, 3076, 2972, 2936, 2877, 1812, 1723, 1643, 1607, 1575, 1540, 1505, 1458, 1382, 1353, 1300, 1254, 1169, 1109, 1074, 1044 and 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.75 (d, 2H, *J*=9.0 Hz), 6.92 (d, 2H, *J*=9.6 Hz), 5.07 (d, 1H, *J*=4.8 Hz), 4.89 (dd, 1H), 4.54 (d, 1H, *J*=10.2 Hz), 4.42–4.30 (m, 3H), 3.85 (s, 3H), 3.70–3.58 (m, 2H), 3.50–3.44 (m, 2H), 3.36–3.30 (m, 5H), 3.30–3.20 (m, 2H), 2.90–2.82 (m, 2H), 2.82–2.78 (m, 1H), 2.48–2.38 (m, 7H), 2.38–2.32 (m, 1H), 2.21 (s, 4H), 2.06–2.02 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.80 (m, 1H), 1.70–1.50 (m, 7H), 1.48–1.40 (m, 5H), 1.32–1.24 (m, 6H), 1.23–1.18 (m, 10H), 1.14 (s, 3H), 1.10–1.02 (m, 6H) and 0.96–0.88 (m, 3H); HRMS (ESI) m/z calculated for $C_{52}H_{87}N_4O_{16}$ ($M+H^+$) 1023.6117, found 1023.6095.

4″-*O*-(((2-methoxybenzamido)butyl)carbamoyl) AZM-11,12-carbonate (6b)

White solid, yield 83.2%, m.p. 166–168 °C, TLC R_f=0.38 (methanol/dichlormethane, 1:10); IR (KBr): 3407, 3077, 2972, 2937, 2877, 1812, 1721, 1649, 1600, 1536, 1484, 1458, 1383, 1353, 1334, 1299, 1278, 1238, 1166, 1109, 1085, 1074, 1046 and 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.98–7.86 (m, 1H), 7.45 (t, 1H, *J*=7.8 Hz), 7.08 (t, 1H, *J*=7.8 Hz), 6.98 (d, 1H, *J*=7.2 Hz), 5.06 (d, 1H, *J*=3.0 Hz), 4.88 (dd, 1H, *J*=9.0 Hz, *J*=6.0 Hz), 4.55 (d, 1H, *J*=9.6 Hz), 4.42–4.30 (m, 3H), 3.97 (s, 3H), 3.68–3.62 (m, 1H), 3.62–3.56 (m, 1H), 3.52–3.44 (m, 2H), 3.36–3.20 (m, 7H), 2.90–2.76 (m, 3H), 2.50–2.30 (m, 8H), 2.19 (s, 4H), 2.06–2.04 (m, 1H), 1.96–1.88 (m, 1H), 1.88–1.78 (m, 3H), 1.68–1.56 (m, 6H), 1.44 (s, 4H), 1.32–1.24 (m, 7H), 1.22–1.16 (m, 9H), 1.15 (s, 3H), 1.10–1.02 (m, 6H) and 0.96–0.86 (m, 3H); HRMS (ESI) m/z calculated for $C_{52}H_{87}N_4O_{16}$ ($M+H^+$) 1023.6117, found 1023.6085.

4″-*O*-(((3,4-dimethoxybenzamido)butyl)carbamoyl) AZM-11,12-carbonate (6c)

White solid, yield 79.9%, m.p. 165–167 °C, TLC R_f=0.34 (methanol/dichlormethane, 1:10); IR (KBr): 3403, 3083, 2972, 2936, 2872, 1812, 1724, 1644, 1603, 1584, 1540, 1507, 1458, 1382, 1352, 1336, 1306, 1269, 1232, 1167, 1126, 1110, 1074, 1045 and 1016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.44 (d, 1H, *J*=1.8 Hz), 7.21 (d, 1H, *J*=7.8 Hz), 6.86 (d, 1H, *J*=8.4 Hz), 5.06 (d, 1H, *J*=3.6 Hz), 4.89 (dd, 1H, *J*=9.6 Hz, *J*=6.0 Hz), 4.55 (d, 1H, *J*=9.6 Hz), 4.42–4.32 (m, 3H), 3.76–3.70 (m, 6H), 3.68–3.56 (m, 2H), 3.52–3.44 (m, 2H), 3.36–3.22 (m, 7H), 2.90–2.72 (m, 3H), 2.50–2.30 (m, 8H), 2.20 (s, 4H), 2.06–2.02 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.80 (m, 1H), 1.76–1.50 (m, 9H), 1.48–1.40 (m, 3H), 1.32–1.24 (m, 6H), 1.24–1.18 (m, 10H), 1.15 (s, 3H), 1.10–1.00 (m, 6H) and 0.94–0.90 (m, 3H); HRMS (ESI) m/z calculated for $C_{53}H_{89}N_4O_{17}$ ($M+H^+$) 1053.6223, found 1053.6183.

4″-*O*-(((4-chlorobenzamido)butyl)carbamoyl) AZM-11,12-carbonate (6d)

White solid, yield 80.5%, m.p. 158–161 °C, TLC R_f=0.40 (methanol/dichlormethane, 1:10); IR (KBr): 3412, 3068, 2972, 2936, 2877, 1812, 1724, 1649, 1596, 1536, 1486, 1457, 1383, 1353, 1314, 1275, 1237, 1167, 1109, 1090, 1074, 1045 and 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.76 (d, 2H, *J*=6.0 Hz), 7.39 (d, 2H, *J*=8.4 Hz), 5.06 (d, 1H, *J*=4.2 Hz), 4.89 (dd, 1H, *J*=9.6 Hz, *J*=6.6 Hz), 4.58–4.50 (m, 1H), 4.42–4.30 (m, 3H), 3.72–3.62 (m, 1H), 3.62–3.54 (m, 1H), 3.52–3.40 (m, 2H), 3.30 (s, 3H), 3.28–3.20 (m, 4H), 2.94–2.86 (m, 3H), 2.54–2.46 (s, 6H), 2.46–2.32 (m, 3H), 2.20 (s, 3H), 2.06–2.02 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.80 (m, 1H), 1.70–1.50 (m, 7H), 1.48–1.40 (m, 5H), 1.32–1.24 (m, 6H), 1.23–1.18 (m, 10H), 1.15 (s, 3H), 1.10–1.00 (m, 6H) and 0.96–0.88 (m, 3H); HRMS (ESI) m/z calculated for $C_{51}H_{84}ClN_4O_{15}$ ($M+H^+$) 1027.5622, found 1027.5605.

4″-*O*-(((2,4-dichlorobenzamido)butyl)carbamoyl) AZM-11,12-carbonate (6e)

White solid, yield 84.3%, m.p. 165–168 °C, TLC R_f=0.34 (methanol/dichlormethane, 1:10); IR (KBr): 3384, 3066, 2971, 2933, 2855, 1811, 1722, 1650, 1617, 1590, 1528, 1452, 1383, 1314, 1237, 1167, 1123, 1105, 1084, 1045 and 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 7.74 (d, 1H, *J*=7.8 Hz), 7.56 (d, 1H, *J*=7.8 Hz), 7.51 (d, 1H, *J*=7.8 Hz), 5.02 (d, 1H, *J*=4.8 Hz), 4.87 (dd, 1H, *J*=9.0 Hz, *J*=6.0 Hz), 4.59 (d, 1H, *J*=7.2 Hz), 4.53 (d, 1H, *J*=9.6 Hz), 4.44–4.36 (m, 2H), 3.80–3.72 (m, 1H), 3.62–3.56 (m, 1H), 3.56–3.40 (m, 4H), 3.30–3.20 (m, 5H), 2.90–2.70 (m, 9H), 2.48–2.42 (m, 1H), 2.38–2.30 (m, 1H), 2.28–2.24 (m, 1H), 2.21 (s, 3H), 2.06–2.02 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.80 (m, 1H), 1.70–1.50 (m, 7H), 1.48–1.40 (m, 5H), 1.32–1.24 (m, 6H), 1.23–1.18 (m, 10H), 1.08–1.04 (m, 3H), 1.02–0.96 (m, 3H) and 0.96–0.88 (m, 6H); HRMS (ESI) m/z calculated for $C_{51}H_{83}Cl_2N_4O_{15}$ ($M+H^+$) 1061.5232, found 1061.5208.

4″-*O*-(((4-nitrobenzamido)butyl)carbamoyl) AZM-11,12-carbonate (6f)

White solid, yield 79.6%, m.p. 125–128 °C, TLC R_f=0.29 (methanol/dichlormethane, 1:10); IR (KBr): 3396, 3067, 2973, 2934, 2873, 2675, 2623, 2605, 2497, 1811, 1723, 1656, 1601, 1526, 1457, 1383, 1348, 1299, 1278, 1237, 1168, 1123, 1108, 1075, 1044 and 1014 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 8.23 (d, 2H, *J*=7.8 Hz), 8.10 (d, 2H, *J*=9.6 Hz), 5.02 (d, 1H, *J*=3.0 Hz), 4.90–4.84 (m, 1H), 4.56–4.48 (d, 1H), 4.41 (s, 1H), 4.30–4.16 (m, 2H), 3.84–3.72 (m, 1H),

3.62–3.36 (m, 3H), 3.36–3.20 (s, 5H), 3.14–3.06 (m, 2H), 2.90–2.70 (m, 9H), 2.50–2.30 (m, 2H), 2.26–2.16 (s, 4H), 2.06–2.02 (m, 1H), 1.96–1.88 (m, 1H, 8–CH), 1.86–1.80 (m, 1H), 1.70–1.50 (m, 7H), 1.48–1.36 (m, 5H), 1.32–1.24 (m, 6H), 1.24–1.12 (m, 10H), 1.12–1.04 (m, 3H) and 1.00–1.02 (m, 9H); HRMS (ESI) m/z calculated for $C_{51}H_{84}N_5O_{17}$ ($M+H^+$) 1038.5862, found 1038.5835.

4″-*O*-(((3,5-dinitrobenzamido)butyl)carbamoyl)AZM-11,12-carbonate (6g)

Slightly yellow solid, yield 83.5%, mp 128–130 °C, TLC R_f=0.28 (methanol/dichlormethane, 1:10); IR (KBr): 3423, 3105, 2972, 2936, 2878, 1812, 1726, 1670, 1629, 1543, 1457, 1382, 1344, 1301, 1277, 1237, 1167, 1110, 1074, 1045 and 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, δ p.p.m.) 9.24–9.18 (m, 2H), 9.18–9.12 (m, 1H), 5.09 (d, 1H, *J*=4.8 Hz), 4.89 (dd, 1H, *J*=9.6 Hz, *J*=6.6 Hz), 4.63 (d, 1H, *J*=9.6 Hz), 4.46–4.30 (m, 3H), 3.70–3.54 (m, 4H), 3.38–3.22 (m, 7H), 2.92–2.82 (m, 2H), 2.78–2.68 (m, 1H), 2.50–2.34 (m, 8H), 2.20 (s, 4H), 2.08–1.50 (m, 10H), 1.48–1.38 (m, 5H), 1.32–1.24 (m, 6H), 1.24–1.14 (m, 10H), 1.12–1.02 (m, 6H) and 0.96–0.88 (m, 6H); HRMS (ESI) m/z calculated for $C_{51}H_{83}N_6O_{19}$ ($M+H^+$) 1083.5713, found 1083.5691 (Supplementary Information).

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RETRACTION

Novel azithromycin derivatives with the C-4″ bisamide side chains: synthesis and biological evaluation against gram-positive bacteria

Wenping Cui, Lihong An, Chenchen Ma, Siti Ma, Chao Cong, Xin Li and Shutao Ma

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The corresponding author has indicated to the journal that this paper should be retracted as it is a duplicate publication. The author apologizes to the journal and its readers for any inconvenience caused.