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Short communication

Synthesis and antibacterial activity of novel 3-*O*-descladinosylazithromycin derivatives

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ABSTRACT

Novel series of novel 3-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives with the 2′-*O*-acetyl and 11,12-cyclic carbonate groups, the 11,12-cyclic carbonate group and the 11-*O*-arylalkylcarbamoyl side chain, and 2′-*O*-arylalkylcarbamoyl descladinosylazithromycin with the 11,12-cyclic carbonate group were designed, synthesized and evaluated for their antibacterial activity using broth microdilution method. The results showed that the majority of the target compounds showed moderate to favorable activity against six kinds of susceptible strains and almost all of them displayed significantly improved activity compared with references against three erythromycin-resistant strains of *S. pneumoniae* B1 expressing the *erm*B gene, *S. pneumoniae* AB11 expressing the *erm*B and *mef*A genes, and *S. pyogenes* R1. In particular, compound **6h** exhibited the most potent activity against susceptible *B. subtilis* ATCC9372 (0.5 μg/mL), penicillin-resistant *S. epidermidis* (0.125 μg/mL), and erythromycin-resistant *S. pneumoniae* B1 (1 μg/mL) and *S. pneumoniae* AB11 (1 μg/mL), which were 2-, 2-, 256-, 256-fold better activity than azithromycin, respectively. Additionally, compounds **6f** (0.5 μg/mL) and **6g** (0.25 μg/mL) were the most active against *S. pneumoniae* A22072, which were 8- and 16-fold better activity than azithromycin (4 μg/mL). As for erythromycin-resistant *S. pyogenes* R1, compound **5a** presented the most excellent activity (8 μg/mL), showing 32- and 32-fold higher activity than azithromycin (256 μg/mL) and clarithromycin (256 μg/mL).

1. Introduction

First generation macrolide antibiotics (e.g. erythromycin A) (Fig. 1) have been introduced for over 60 years and been used in treating upper and lower respiratory tract infections in clinic [1,2]. However, erythromycin A (EMA) can degrade under the acidic conditions of stomach, and the resultant 6,9-hemiketal degradation products might result in gastrointestinal side effects and poor bioavailability [3]. To approach the acid instability of EMA, scientists developed the second generation macrolides such as azithromycin and clarithromycin (Fig. 1) with improved antibacterial activity and pharmacokinetic properties compared with EMA [4].

However, the therapeutic utility of the macrolide antibiotics has been limited by the emergence of bacterial resistance. The two main mechanisms of resistance are target modification mediated by *erm*B gene and drug efflux mediated by *mef*A gene, respectively. A methyl transferase encoded by the *erm* gene can dimethylate the nucleotide A2058 of 23S rRNA in bacterial ribosome, thereby leading to no interaction between the macrolide antibiotics and the ribosome [5–7]. The *erm*B-positive bacterial strains showed cross resistance to macrolides, lincosamides and streptogramin B (MLS_B) antibiotics. As for the second mechanism, an efflux transporter encoded by the *mef* gene can pump the macrolides out of the bacterial cell [8].

The emergence and prevalence of resistant pathogens makes it an urgent need to investigate new antibacterial agents. Consequently, the third-generation macrolides such as ketolides are discovered [4,9]. The C-6 side chain or the C-11,12 cyclic carbamate side chain of ketolides (e.g., telithromycin and cethromycin) (Fig. 1) can interact with the nucleotide A752 in domain II of 23S rRNA in addition to binding to the nucleotide A2058 in domain V of the 23S rRNA. These interactions result in tighter affinity for bacterial ribosomes. Therefore, the ketolides can exhibit strong activity

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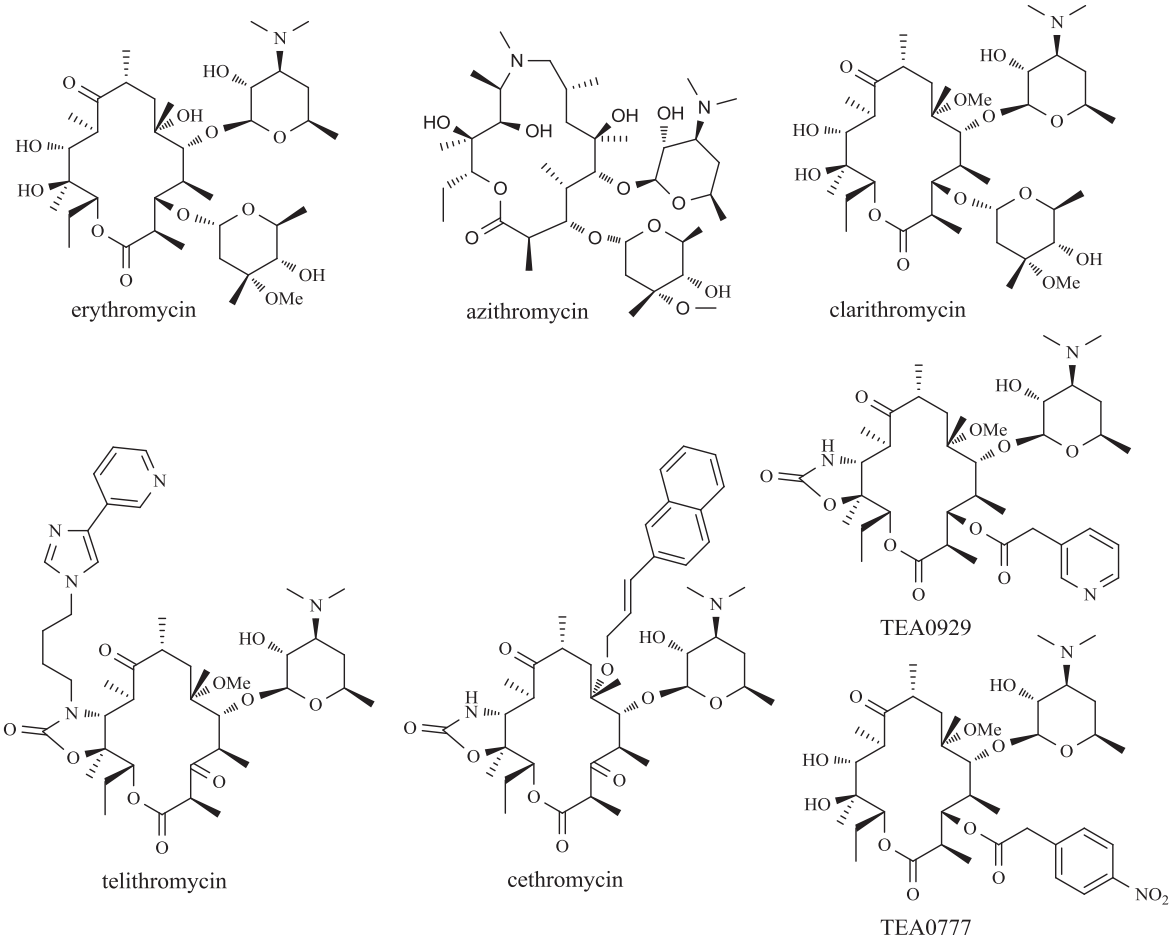

Fig. 1. Structures of erythromycin, azithromycin, clarithromycin, telithromycin, cethromycin, TEA0929 and TEA0777.

against the *erm*B-positive bacterial strains whose ribosomes are methylated [10–12].

An X-ray cocrystal structure research has revealed that macrolide antibiotics bind at the entrance to the peptide exit tunnel in the 23S rRNA of the 50S ribosomal subunit, and its cladinose fits tightly over the base planes formed by G2505, C2610 and C2611 in domain V [13]. For that reason, a new class of macrolide antibiotics called acylides have been discovered. For instance, TEA0929 and TEA0777 (Fig. 1) hopefully shows excellent activity against efflux-resistant *S. pneumoniae* in addition to MLS_B-resistant *S. aureus* [14,15]. The discovery of the acylides represented one of the most important breakthroughs in the process of developing novel macrolides to overcome the *mef*-mediated bacterial resistance effectively [16].

Based on the considerations detailed above, we designed and synthesized four series of novel 3-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives with the 2′-*O*-acetyl and 11,12-cyclic carbonate groups (**4a-h**), the 11,12-cyclic carbonate group (**5a-m**) and the 11-*O*-arylalkylcarbamoyl side chain (**6a-i**), and 2′-*O*-arylalkylcarbamoyl descladinosylazithromycin with the 11,12-cyclic carbonate group (**8a-h**) to prevent the *erm*- or *mef*-mediated bacteria and broaden their antibacterial spectra. The 3-*O*-arylalkylcarbamoyl side chain attached to the descladinosylazithromycin skeleton was not only to inhibit the hydrolysis of the 3-*O*-acyl group on the acylides in the body, but also was liable to interact with the binding pocket composed of G2505, C2610 and C2611 in domain V. On the other hand, the C-11,12 cyclic carbonate group or 11-*O*-arylalkylcarbamoyl side chain introduced to the descladinosylazithromycin skeleton was excepted to bind with A752 in domain II through hydrogen bonding, π-stacking or electrostatic interactions [17–19]. In addition, 2′-*O*-arylalkylcarbamoyl derivatives were also designed, synthesized and evaluated for their antibacterial activity mainly to explore their structure–activity relationships that have not been reported so far [20,21].

2. Chemistry

2.1. Synthesis of 11,12-cyclic carbonate descladinosylazithromycin 2′-*O*-acetyl-3-*O*-arylalkylcarbamoyl derivatives

The synthetic method for 11,12-cyclic carbonate descladinosylazithromycin 2′-*O*-acetyl-3-*O*-arylalkylcarbamoyl derivatives is shown in Scheme 1. Selective cleavage of the 3-*O*-sugar moiety from AZM with 1M aqueous hydrochloric acid (HCl) and subsequent protection of the 2'-hydroxyl group with acetic anhydride (Ac_2O) in the presence of triethylamine (Et_3N) gave 2'-acetate product (**2**) [22,23]. 11,12-Carbonate 2′-*O*-acetyl-3-*O*-acylimidazolide **3** was prepared in toluene at 55 °C by treatment of **2** with CDI in the presence of triethylamine. 2′-*O*-acetyl-3-*O*-arylalkylcarbamoyl derivatives (**4a-h**) were obtained in 62–71% yields by condensation of **3** with the corresponding arylamines in the presence of pyridine hydrochloride [24,25].

2.2. Synthesis of 11,12-cyclic carbonate descladinosylazithromycin 3-*O*-arylalkylcarbamoyl derivatives

The synthetic method for 11,12-cyclic carbonate descladinosylazithromycin 3-*O*-arylalkylcarbamoyl derivatives is shown in

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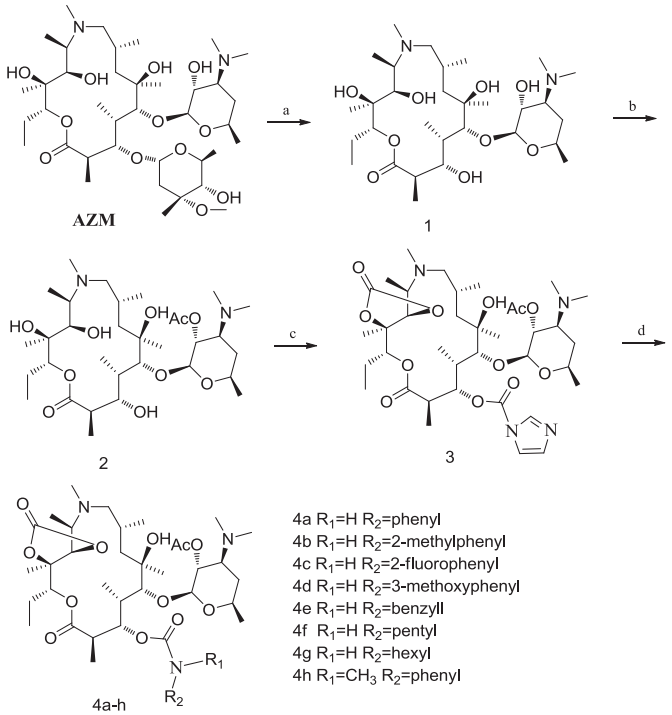
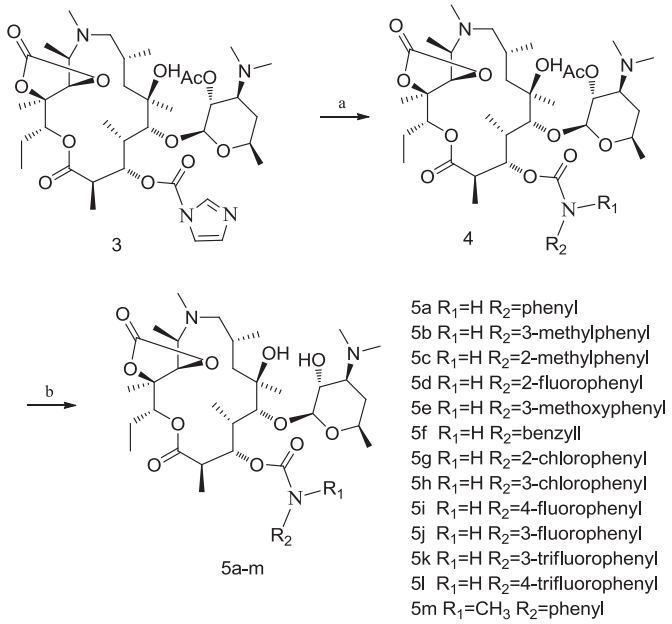


Scheme 1. Synthetic route for 11,12-cyclic carbonate descladinosylazithromycin 2′-*O*-acetyl-3-*O*-arylalkylcarbamoyl derivatives **4a-h**. Regents and Conditions: (a) 1M HCl, CH_3OH; (b) $(CH_3CO)_2O$, CH_2Cl_2, Et_3N, rt, 24 h; (c) CDI, Et_3N, toluene, 55 °C, 72 h; (d) R_1NH_2, pyridine hydrochloride, rt, 6–8 days.

Scheme 2. 11,12-Carbonate 2′-*O*-acetyl-3-*O*-acylimidazolide **3** was prepared in toluene at 55 °C by treatment of **2** with CDI in the presence of triethylamine. 3-*O*-Arylalkylcarbamoyl descladinosylazithromycin derivatives (**5a-m**) were obtained in 62–71% yields by condensation of **3** with the corresponding arylamines in the presence of pyridine hydrochloride, followed by selective removal of the 2′-*O*-acetyl group by heating with methanol [26].



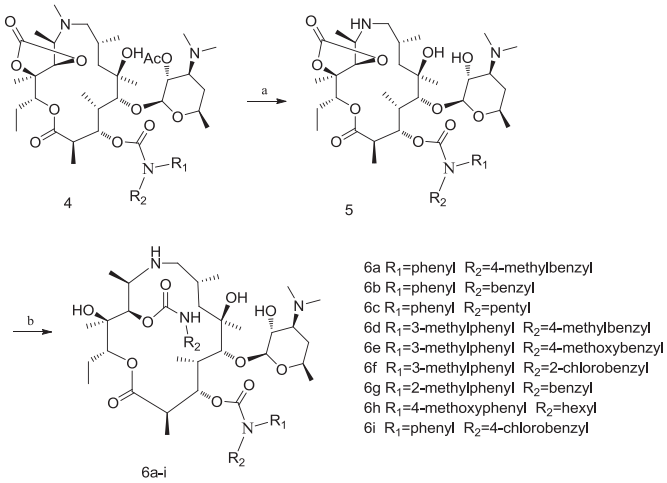
Scheme 2. Synthetic route for 11,12-cyclic carbonate descladinosylazithromycin 3-*O*-arylalkylcarbamoyl derivatives **5a-m**. Regents and Conditions: (a) R_1NH_2, pyridine hydrochloride, rt, 6–8 days; (b) CH_3OH, 55 °C, 12 h.

2.3. Synthesis of 11,3-di-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives

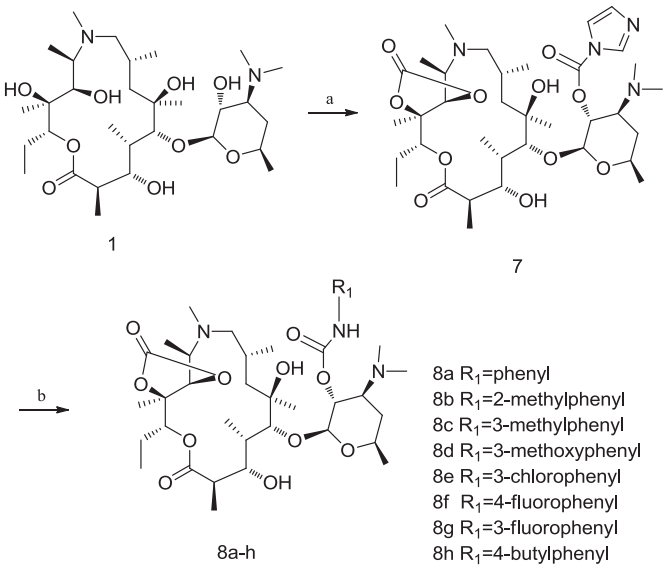
11, 3-Di-*O*-arylalkylcarbamoyl descladinosylazithromycin derivativesc were synthesized from compound **4** (Scheme 3). Compound **4** with an aromatic side chain at the 3-position was deprotected and then readily converted to novel 11,3-di-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives (**6a-i**) by reacting with the corresponding amines in the presence of pyridine hydrochloride.

2.4. Synthesis of 11,12-cyclic carbonate descladinosylazithromycin 2′-*O*-arylalkylcarbamoyl derivatives

Treatment of descladinosylazithromycin **1** with CDI in the presence of trimethylamine in toluene provided 11,12-carbonate 2′-*O*-acylimidazolide **7**. And then the reaction of **7** with the corresponding amines in the presence of pyridine hydrochloride produced novel 11,12-cyclic carbonate descladinosylazithromycin 2′-



Scheme 3. Synthetic route for 11,3-di-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives **6a-i**. Regents and Conditions: (a) CH_3OH, 55 °C, 12 h; (b) R_2NH_2, pyridine hydrochloride, rt, 72 h.



Scheme 4. Synthetic route for 11,12-cyclic carbonate descladinosylazithromycin 2′-*O*-arylalkylcarbamoyl derivatives **8a-h**. Regents and Conditions: (a) CDI, Et_3N, toluene, 55 °C, 72 h; (b) R_1NH_2, pyridine hydrochloride, rt, 6–8 days.

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O-arylalkylcarbamoyl derivatives (**8a-h**) (Scheme 4).

3. Antibacterial evaluation

All the compounds synthesized above were evaluated for their *in vitro* antibacterial activity by the broth microdilution method recommended by NCCL [10]. Minimal inhibitory concentration (MIC) values for all compounds were determined in comparison with AZM and CLA on a panel of susceptible and resistant Gram-positive strains that are *Staphylococcus aureus* ATCC25923 (erythromycin-susceptible strain), *Streptococcus pyogenes* (erythromycin-susceptible strain isolated clinically), *Escherichia. coli* ATCC25922 (penicillin-susceptible strain), *Staphylococcus Epidermidis* (penicillin-resistant strain isolated clinically, not characterized), *Bacillus subtilis* ATCC9372 (penicillin-susceptible strain), *Pseudomonas aeruginosa* ATCC27853 (penicillin-susceptible strain), *S. aureus* ATCC29213 (methicillin-resistant strain), *S. pneumoniae* B1 (erythromycin-resistant strain expressing the *erm* gene), *S. pneumoniae* A22072 (erythromycin-resistant strain expressing the *mef* gene), *S. pneumoniae* AB11 (erythromycin-resistant strain expressing the *erm* and *mef* genes), *S. pyogenes* R1 (erythromycin-resistant strain isolated clinically). Their MIC results are shown in Table 1.

4. Results and discussion

11,12-Cyclic carbonate azithromycin 2′-*O*-acetyl-3-*O*-arylalkylcarbamoyl derivatives **4a-h** showed slightly improved antibacterial activity against *S. pneumoniae* expressing the *erm*B gene, *S. pneumoniae* expressing the *erm*B and *mef*A genes, and erythromycin-resistant *S. pyogenes* R1. Among them, the most

Table 1
3-*O*-Descladinosylazithromycin derivatives with their *in vitro* antibacterial activity against susceptible and resistant strains (μg/mL).

Compound	*S. aureus* ATCC 25923[a]	*E. coli* ATCC 25922[b]	*S. pyogenes*[c]	*P. aeruginosa* ATCC 27853[d]	*B. subtilis* ATCC 9372[e]	*S. epidermidis*[f]	*S. aureus* ATCC 29213[g]	*S. pneumoniae* B1[h]	*S. pneumoniae* A22072[i]	*S. pneumonae* AB11[j]	*S. pyogenes* R1[k]
3	128	32	8	128	128	128	128	256	16	256	56
4a	32	32	0.25	64	32	16	128	128	4	64	128
4b	16	64	1	64	8	128	64	256	8	16	256
4c	32	64	4	128	32	64	64	128	8	32	128
4d	32	64	2	64	16	32	64	128	16	32	128
4e	64	128	8	128	64	64	64	128	32	64	128
4f	32	128	4	128	32	32	64	64	32	128	128
4g	16	128	4	128	8	16	32	64	64	16	32
4h	ND	ND	ND	ND	ND	128	ND	ND	ND	ND	ND
5a	2	128	0.25	128	4	4	128	16	16	16	8
5b	2	64	1	64	8	4	64	64	8	16	32
5c	4	64	0.5	64	2	4	32	32	4	1	32
5d	8	64	0.5	64	32	4	64	64	16	16	64
5e	16	64	2	64	16	32	64	64	16	16	64
5f	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
5g	8	128	0.125	128	8	64	64	64	1	4	128
5h	8	128	0.25	128	16	0.5	64	32	1	4	32
5i	32	128	0.25	128	16	64	64	32	2	8	64
5j	32	128	2	128	128	64	128	64	16	32	128
5k	16	128	1	128	64	0.5	128	32	8	8	64
5l	16	128	1	128	32	0.25	128	32	4	4	64
5m	4	64	0.125	64	4	8	64	64	2	4	64
6a	32	128	4	128	32	16	128	64	16	64	64
6b	32	64	2	64	8	32	128	128	16	2	64
6b	16	64	1	64	4	16	64	64	8	4	64
6d	8	64	4	64	8	4	128	64	32	16	32
6e	16	128	1	128	16	32	128	128	8	16	128
6f	2	64	0.03	64	4	0.25	64	8	0.5	4	32
6g	1	64	0.03	64	2	0.25	32	32	0.25	2	128
6h	8	128	1	128	0.5	0.125	128	1	8	1	32
6i	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
7	64	64	8	64	128	32	128	256	128	32	256
8a	32	64	0.5	32	32	32	128	128	8	8	128
8b	4	64	0.5	64	4	16	32	64	2	4	64
8c	32	64	1	128	32	32	128	128	128	64	64
8d	32	64	2	64	128	64	128	128	16	32	128
8e	16	32	1	64	8	32	128	64	8	32	64
8f	16	128	1	128	64	64	128	64	4	8	64
8g	32	128	1	128	128	64	128	256	8	16	128
8h	32	128	8	128	128	64	128	256	64	32	64
AZM	0.25	64	0.03	32	1	0.25	4	256	4	256	256
CLA	0.25	32	0.03	64	0.25	0.25	32	256	2	128	256

[a] *S. aureus* ATCC25923: erythromycin-susceptible strain.
[b] *E. coli* ATCC25922: penicillin-susceptible strain.
[c] *S. pyogenes*: erythromycin-susceptible strain isolated clinically.
[d] *P. aeruginosa* ATCC27853: penicillin-susceptible strain.
[e] *B. subtilis* ATCC9372: erythromycin-susceptible strain.
[f] *S. epidermidis*: penicillin-resistant strain isolated clinically, not characterized.
[g] *S. aureus* ATCC29213: methicillin-resistant strain.
[h] *S. pneumoniae* B1: erythromycin-resistant strain encoded by the *erm*B gene.
[i] *S. pneumoniae* A22072: erythromycin-resistant strain encoded by the *mef*A gene.
[j] *S. pneumoniae* AB11: erythromycin-resistant strain encoded by the *erm*B and *mef*A genes.
[k] *S. pyogenes* R1: erythromycin-resistant strain isolated clinically.

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active compound **4g** showed 8-fold more potent antibacterial activity against resistant erythromycin-resistant *S. pyogenes* R1 than references. However, all of compounds **4a-h** failed to show better antibacterial activity than AZM against four susceptible strains of *S. aureus* ATCC 25923, *S. pyogenes*, *P. aeruginosa* ATCC27853, *B. subtilis* ATCC9372 and two resistant strains of penicillin-resistant *S. epidermidis* and methicillin-resistant *S. aureus.*

11,12-Cyclic carbonate descladinosylazithromycin 3-*O*-arylalkylcarbamoyl derivatives **5a-m** showed obviously increased activity against four types of resistant strains. Among them, compound **5a** was the most effective against erythromycin-resistant *S. pneumoniae* B1 and *S. pyogenes* R1, showing 16- and 32-fold better antibacterial activity than references, respectively. In addition, compounds **5l** (0.25 μg/mL) and **5c** (32 μg/mL) were the most active against penicillin-resistant *S. epidermidis* and methicillin-resistant *S. aureus* respectively, equivalent to CLA. As for other susceptible *S. aureus, E. coli*, *S. pyogenes*, *P. aeruginosa* and *B. subtilis*, however, this series did not show notably improved antibacterial activity compared with references. The above results indicated that introduction of the 3-*O*-arylalkylcarbamoyl group could result in better binding to the ribosomes of macrolide-resistant bacteria.

In the series of 11,3-di-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives **6a-h**, some compounds showed potent antibacterial activity superior or equal to that of AZM against susceptible *E. coli*, *S. pyogenes*, and *B. subtilis*. For example, compounds **6f-h** demonstrated significantly improved antibacterial activity against *S. pneumoniae* expressing the *erm*B gene, the *mef*A gene, and the *erm*B and *mef*A genes, showing 8-—256-fold better activity than references. As for susceptible *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 and resistant *S. aureus* ATCC 29213, this series did not present antibacterial activity equal to AZM. The above results clearly indicated that introduction of an arylalkylcarbamoyl group into the 11-position of the 3-*O*-arylalkylcarbamoyl derivatives dramatically enhanced their antibacterial activity against the *erm*-resistant *S. pneumoniae* and the *mef*-resistant *S. pneumoniae.*

11,12-Cyclic carbonate descladinosylazithromycin 2′-*O*-arylalkylcarbamoyl derivatives **8a-h** exhibited increased activity against *S. pneumoniae* expressing the *erm*B gene, the *mef*A gene and the *erm*B and *mef*A genes, and erythromycin-resistant *S. pyogenes* R1, as well as medium antibacterial activity against susceptible *S. aureus* ATCC 25923, *S. pyogenes*, *B. subtilis* ATCC9372 and penicillin-resistant *S. epidermidis* and methicillin-resistant *S. aureus* compared with references. Particularly, compounds **8e** and **8a** presented the best antibacterial activity against Gram-negative *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853, respectively in all of the 40 tested compounds. This indicated that the introduction of 2′-*O*-arylalkylcarbamoyl group could enhance antibacterial activity against Gram-negative bacteria.

On the whole, a majority of the target compounds showed moderate to favorable activity against six kinds of susceptible strains. Among them, compound **6g** was found to have the most potent antibacterial activity (1 μg/mL) against *S. aureus* ATCC25923 and compounds **3**, **4a** and **8e** were the most effective (32 μg/mL) against *E. coli* ATCC25922 comparable to CLA (32 μg/mL) and AZM (64 μg/mL). Additionally, compounds **4a**, **5a**, **5c**-**5d**, **5g-i**, **5m**, **6f-g** and **8a-b** also displayed outstanding activity against susceptible *S. pyogenes*, with MIC values between 0.03 and 0.5 μg/mL. Compound **6h** was the most effective (0.5 μg/mL) against *B. subtilis* ATCC9372, showing 2-fold higher activity than AZM. Unfortunately, only compound **8a** among all of the target compounds exhibited similar activity to AZM against *P. aeruginosa* ATCC27853.

On the other hand, compound **6h** with the 4-methoxylphenylcarbamoylaryl group at the 3-position and the *n*-hexylcarbamoyl group at the 11-position exerted the highest antibacterial activity (0.125 μg/mL) against penicillin-resistant *S. epidermidis*, superior to references (0.25 μg/mL) and compounds **5l**, **6f** and **6g** also exhibited potent antibacterial activity with the same MIC values of 0.5 μg/mL against resistant *S. epidermidis*, comparable to the references. In remarkable contrast, none of the compounds showed improved antibacterial activity against methicillin-resistant *S. aureus* compared with AZM and CLA.

Surprisingly, most of the tested compounds showed significantly improved activity compared with AZM and CLA against resistant *S. pyogenes* and all the three phenotypes of resistant *S. pneumoniae*. For instance, the most active compound **6h** (1 μg/mL) against *S. pneumoniae* expressing the *erm*B gene, exhibited 256-fold enhanced activity than the references, and compounds **6f** (0.5 μg/mL) and **6g** (0.25 μg/mL) displayed the most excellent activity against *S. pneumoniae* expressing the *mef*A gene, which were 8- and 16-fold better than that of azithromycin. Besides, compounds **5g-i**, **5m** and **8b** also demonstrated strong activity against *S. pneumoniae* expressing the *mef*A gene, with MIC values of 1—2 μg/mL. In addition, compounds **5c** and **6h** shared the identical activity with the MIC value of 1 μg/mL against *S. pneumoniae* expressing the *erm*B and *mef*A genes, which was 256 and 128-fold better than that of AZM (256 μg/mL) and CLA (128 μg/mL), respectively. As for erythromycin-resistant *S. pyogenes*, compound **5a** was effective (8 μg/mL), showing 32-fold higher activity than references (256 μg/mL).

In particular, compound **6f** with the C-11 arylalkylcarbamoyl group displayed 8-, 16-fold more potent activity than its precursor **5b** against *erm*-resistant *S. pneumoniae* expressing the *erm*B gene and the *mef*A gene, respectively, and compounds **6g** (0.25 μg/mL) with the C-11 arylalkylcarbamoyl group exhibited 16-fold greater activity than its precursor **5c** (4 μg/mL) against *S. pneumoniae* expressing the *mef*A gene.

On the basis of all of results, we speculated that the C-11-arylalkylcarbamoyl side chain could interact with the nucleotide A752 directly in domain II of the 23S rRNA, and the 3-*O*-arylalkylcarbamoyl side chain could bind to the nucleotide G2505, C2610 or C2611 in domain V in addition to the interaction of its descladinosylazithromycin nucleus with the nucleotide A2058 in domain V, which brought about an additional affinity for the resistant ribosome, resulting in increased activity against the resistant bacteria.

Moreover, we performed a molecular docking study on compound **5b** using the SYBYL-X 2.0to further understand the interaction of 3-*O*-carbamoyl descladinosylazithromycin derivatives with 23S rRNA of 50S ribosomal subunit. We retrieved the crystal structure of the 50S ribosomal subunit of Deinococcus radiodurans in complex with azithromycin from the deposited PDB structure 1nwy. The binding mode of **5b** was listed in Fig. 2. The result indicated that a hydrogen bond was formed between the 3-*O*-carbamoyl of compound **5b** and C2589 (C2610 in *E. coli*).

5. Conclusion

Novel 2′, 3-di-*O*-substituted 11,12 cyclic carbonate, 3-*O*-arylalkylcarbamoyl 11,12 cyclic carbonate, 3,11-*O*-arylalkylcarbamoyl, and 2′-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives were designed, synthesized and tested for their *in vitro* antibacterial activity against various phenotypes of Gram-positive and Gram-negative bacteria species. Generally, the majority of the target compounds displayed moderate to favorable activity against six kinds of susceptible strains, and significantly improved activity against all of the four erythromycin-resistant strains, *S. pneumoniae* B1, *S. pneumoniae* A22072, *S. pneumoniae* AB11 and *S. pyogenes* R1 compared with references. 2′-*O*-Arylalkylcarbamoyl 11,12-cyclic carbonate derivatives **8e** and **8a** presented the best antibacterial activity against Gram-negative *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853, respectively, in all of the 40 target compounds.

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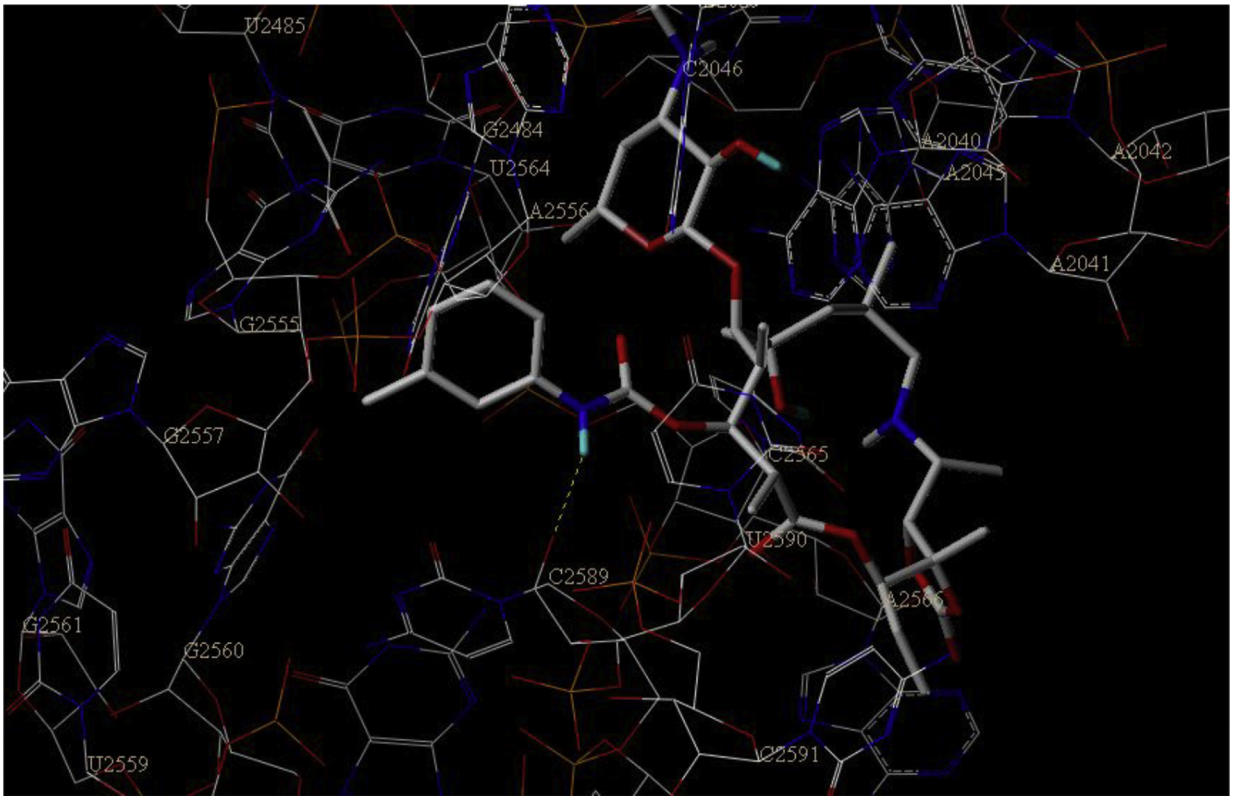

Fig. 2. The stereo view of the docking poses of **5b**. The gray and color moiety represents compound **5b**. The dotted yellow line represents hydrogen bond. The fine lines represents nucleotides. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Compound **5a** possessed potent activity (8 μg/mL) against erythromycin-resistant *S. pyogenes*, showing 32-fold higher activity than references (256 μg/mL). Compound **6h** exhibited the highest antibacterial activity against susceptible *B. subtilis* ATCC9372 (0.5 μg/mL), penicillin-resistant *S. epidermidis* (0.125 μg/mL), the *erm*-resistant *S. pneumoniae* (1 μg/mL), the *erm* and *mef*-resistant *S. pneumoniae* (1 μg/mL). Besides, 11,3-*O*-arylalkylcarbamoyl derivatives **6f-g** showed better antibacterial activity than 11,12-cyclic carbonate 3-*O*-arylalkylcarbamoyl derivatives **5b-c** against the *erm*-resistant *S. pneumoniae* and the *mef*-resistant *S. pneumoniae*. The molecular docking study indicated that the 3-*O*-arylalkylcarbamoyl side chain in the descladinosylazithromycin nucleus could interact with the cavity formed by G2505, C2610 and C2611 in domain V, resulting in a higher affinity to bacterial ribosomes. The above findings demonstrated that introduction of the C-11 arylalkylcarbamoyl side chain dramatically enhanced antibacterial activity against erythromycin-resistant strains.

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). 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. 2′-*O*-Acetyl-3-*O*-descladinosylazithromycin (**2**)

To a solution of azithromycin (2.0 g, 2.67 mmol) in absolute ethanol (20 mL) at room temperature was added dropwise 1 M HCl (9 mL). The resulting solution was allowed to stir for 20 h at the same temperature. And then, the reaction solution was neutralized to pH value 10.5–11.0 with 1 M sodium hydroxide and stirred for 2 h at the room temperature. The resulting precipitate was filtered, washed with cool water, dried to afford 1.1 g (69%) of 3-*O*-descladinosylazithromycin as a white solid: mp 138–141 °C, R_f = 0.3 (dichloromethane/methanol, 10:1, v/v).

To a solution of 3-*O*-descladinosylazithromycin (1.0 g, 1.69 mmol) in dichloromethane (10 mL) at room temperature was added acetic anhydride (0.33 mL, 3.50 mmol) and Et_3N (1.00 mL, 7.20 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, dried to afford 0.8 g (75%) mp 143–145 °C; R_f = 0.41 (dichloromethane/methanol, 10:1).

6.2. 2′-*O*-Acetyl-3-*O*-acylimidazolyl descladinosylazithromycin 11,12-cyclic carbonate (**3**)

To a solution of **2** (0.6 g, 0.95 mmol) in toluene (8 mL) was added

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Et_3N (0.62 mL, 4.50 mmol) and CDI (0.62 g, 3.83 mmol). The resulting solution was heated to 55 °C and stirred at the same temperature for 72 h. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and the aqueous layer was extracted with toluene (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography (dichloromethane/methanol, 20:1) to afford 0.7 g (75%) of **3** as a white solid: mp 149–152 °C; $R_f = 0.45$ (dichloromethane/methanol, 10:1).

6.3. General methods for the preparation of 11,12-cyclic carbonate descladinosylazithromycin 2′-O-acetyl-3-O-arylalkylcarbamoyl derivatives (**4a-h**)

Compound **3** were readily converted to 11,12-cyclic carbonate descladinosylazithromycin 2′-*O*-acetyl-3-*O*-arylalkylcarbamoyl derivatives (**4a-h**) by coupling with the corresponding amines in the presence of pyridine hydrochloride at room temperature for 6–8 days in yields ranging from 58% to 69%. $R_f = 0.7$ (dichloromethane/methanol, 10:1).

6.4. General methods for the preparation of 11,12-cyclic carbonate descladinosylazithromycin 3-O-arylalkylcarbamoyl derivatives (**5a-m**)

A solution of the above crude product **4** in methanol (15 mL) was heated to 50 °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, 40:1, v/v) to afford the desired products **5a-m**.

6.5. General methods for the preparation of 11,3-di-O-arylalkylcarbamoyl descladinosylazithromycin derivatives (**6a-i**)

Compound **5** were readily converted to 11,3-di-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives (**6a-i**) by coupling with the corresponding amines in the presence of pyridine hydrochloride at room temperature for 6–8 days. The crude product was purified by flash chromatography (dichloromethane/methanol, 6:1, v/v), $R_f = 0.2$ (dichloromethane/methanol, 10:1). The yields ranged from 45% to 54%.

6.6. General methods for the preparation of (**8a-h**)

To a solution of azithromycin (2.0 g, 2.67 mmol) in absolute ethanol (20 mL) at room temperature was added dropwise 1 M HCl (9 mL). The resulting solution was allowed to stir for 20 h at the same temperature. And then, the reaction solution was neutralized to pH value 10.5–11.0 with 1 M sodium hydroxide and stirred for 2 h at the room temperature. The resulting precipitate was filtered, washed with cool water, dried to afford 1.1 g (69%) of 3-*O*-descladinosylazithromycin as a white solid: mp 138–141 °C, $R_f = 0.3$ (dichloromethane/methanol 10:1, v/v).

To a solution of 3-*O*-descladinosylazithromycin (0.56 g, 0.95 mmol) in toluene (8 mL) was added Et_3N (0.62 mL, 4.50 mmol) and CDI (0.62 g, 3.83 mmol). The resulting solution was heated to 55 °C and stirred at the same temperature for 48 h. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and the aqueous layer was extracted with toluene (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography (dichloromethane/methanol, 40:1) to afford 0.15 g (75%) of **7** as a white solid: mp 148–150 °C; $R_f = 0.6$ (dichloromethane/methanol, 10:1).

Compound **7** were readily converted to 2′-*O*-arylalkylcarbamoyl descladinosylazithromycin derivatives (**8a-h**) by coupling with the corresponding amines in the presence of pyridine hydrochloride at room temperature for 6–8 days. The crude product was purified by flash chromatography (dichloromethane/methanol, 50:1, v/v), $R_f = 0.75$ (dichloromethane/methanol, 10:1). The yields ranged from 60% to 75%.

6.6.1. 11,12-Carbonate 2′-O-acetyl-3-O-acylimidazolide descladinosylazithromycin derivative (**3**)

White solid, yield 62%, mp 149–152 °C, TLC $R_f = 0.45$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.52 (s, 1H), 7.19–7.15 (m, 1H), 5.71 (m,, 1H), 4.69 (m, 2H), 4.02 (m, 1H), 3.58 (m, 1H), 3.28–3.07 (m, 1H), 2.86 (m, 1H), 2.65 (m, 1H), 2.37 (m, 1H), 2.27 (s, 4H), 2.19 (s, 7H), 2.09 (s, 4H), 1.51 (m, 2H), 1.44 (s, 3H), 1.33–1.19 (m, 9H), 1.09 (m, 10H), 0.91 (s, 7H). MS (ESI) *m/z* calcd. for $C_{37}H_{60}N_4O_{12}$ 752.4; found $[M + H]^+$ 753.7.

6.6.2. 11,12-Carbonate 2′-O-acetyl-3-O-(phenyl)carbamoyl descladinosylazithromycin derivative (**4a**)

White solid, yield 62%, mp 120–123 °C, TLC $R_f = 0.7$ (CH_2Cl_2:MeOH = 10:1);^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 2H), 7.33 (s, 2H), 7.07 (s, 1H), 6.15 (s, 1H), 5.11–5.08 (m, 1H), 4.71 (s, 1H), 4.62 (s, 1H), 4.25 (s, 1H), 3.60–3.57 (s, 1H), 3.13 (s, 1H), 2.90 (s, 1H), 2.83 (d, $J = 5.9$ Hz, 1H), 2.51 (s, 1H), 2.35 (s, 1H), 2.27 (s, 4H), 2.18–2.15 (m, 11H), 2.06 (s, 2H), 2.02 (s, 1H), 1.87 (s, 2H), 1.42 (s, 4H), 1.25 (d, $J = 5.3$ Hz, 5H), 1.21 (s, 4H), 1.17 (s, 1H), 1.06 (s, 6H), 0.98 (d, $J = 5.8$ Hz, 3H), 0.91 (d, $J = 6.0$ Hz, 7H). MS (ESI) *m/z* calcd. for $C_{40}H_{63}N_3O_{12}$ 777.4; found $[M + H]^+$ 778.7.

6.6.3. 11,12-Carbonate 2′-O-acetyl-3-O-(2-methylphenyl) carbamoyl descladinosylazithromycin derivative (**4b**)

White solid, yield 78%, mp 124–126 °C, TLC $R_f = 0.7$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–6.21 (m, 4H), 4.62 (s, 1H), 3.61 (s, 1H), 2.94 (s, 1H), 2.84 (s, 1H), 2.32 (s, 4H), 2.28 (s, 5H), 2.23 (s, 1H), 2.20 (s, 1H), 2.13 (s, 3H), 2.06 (s, 2H), 2.02 (s, 3H), 1.45–1.43 (m, 3H), 1.26 (s, 17H), 1.15 (s, 2H), 1.08 (s, 5H), 1.00 (s, 2H), 0.91 (s, 8H). MS (ESI) *m/z* calcd. for $C_{41}H_{65}N_3O_{12}$ 791.5; found $[M + H]^+$ 792.7.

6.6.4. 11,12-Carbonate 2′-O-acetyl-3-O-(2-fluorophenyl)carbamoyl descladinosylazithromycin derivative (**4c**)

White solid, yield 66%, mp 120–122 °C, TLC $R_f = 0.7$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20–8.05 (m, 1H), 7.57–7.37 (m, 1H), 7.18–7.12 (m, 1H), 7.10–7.08 (m, 1H), 7.05–7.03 (m, 1H), 5.19–5.12 (m, 1H), 4.95–4.93 (m, 1H), 4.80–4.77 (m, 1H), 4.55–4.36 (m, 1H), 4.22–4.05 (m, 2H), 3.56–3.34 (m, 1H), 3.09–2.82 (m, 3H), 2.64–2.52 (m, 1H), 2.30–2.27 (m, 3H), 2.22–2.18 (m, 3H), 2.13–2.05 (m, 5H), 2.03–2.01 (m, 2H), 1.98–1.90 (m, 2H), 1.86–1.82 (m, 1H), 1.76–1.71 (m, 3H), 1.66–1.63 (m, 1H), 1.51–1.46 (m, 2H), 1.38–1.20 (m, 8H), 1.17–1.12 (m, 2H), 1.09–0.83 (m, 14H). HRMS (AP-ESI) *m/z* calcd for $C_{40}H_{62}FN_3O_{12}$ $[M + H]^+$ 796.4390, found 796.4448.

6.6.5. 11,12-Carbonate 2′-O-acetyl-3-O-(3-methoxylphenyl) carbamoyl descladinosylazithromycin derivative (**4d**)

White solid, yield 56%, mp 121–123 °C, TLC $R_f = 0.7$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (m, 1H), 7.10 (s, 1H), 6.95 (s, 1H), 6.63 (s, 1H), 5.10 (s, 1H), 4.62 (s, 1H), 4.24 (s, 1H), 3.81 (s, 3H), 3.60 (s, 1H), 2.83 (s, 1H), 2.39 (s, 1H), 2.34 (s, 1H), 2.27 (s, 3H), 2.20 (s, 5H), 2.15 (s, 2H), 2.06 (s, 1H), 1.87 (s, 1H), 1.47 (s, 1H), 1.42 (s, 3H), 1.25 (s, 14H), 1.21 (s, 4H), 1.10–1.06 (s, 6H), 0.97 (d, $J = 5.7$ Hz, 2H), 0.91 (s, 8H). HRMS (AP-ESI) *m/z* calcd for $C_{41}H_{65}N_3O_{13}$ $[M + H]^+$ 808.4589, found 808.4578.

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*6.6.6. 11,12-Carbonate 2′-O-acetyl-3-O-(benzyl)carbamoyl descladinosylazithromycin derivative (**4e**)*

White solid, yield 58%, mp 122–124 °C, TLC R_f = 0.7 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, CDCl3) δ 7.33 (s, 3H), 7.30 (s, 2H), 4.91–4.83 (m, 1H), 4.53 (s, 1H), 4.48–4.44 (m, 2H), 4.31–4.28 (m, 1H), 4.03–4.01 (m, 1H), 3.59–3.51 (m, 1H), 3.25–3.15 (m, 1H), 3.00 (s, 1H), 2.84 (s, 1H), 2.65–2.52 (m, 3H), 2.36–2.24 (m, 7H), 2.20 (s, 2H), 2.06 (s, 2H), 2.03 (s, 2H), 1.95–1.90 (m, 2H), 1.80–1.75 (m, 2H), 1.67 (s, 1H), 1.46–1.40 (m, 3H), 1.26 (s, 10H), 1.16–1.15 (m, 3H), 1.09–1.06 (m, 5H), 0.93–0.88 (m, 7H). MS (ESI) *m*/*z* calcd. for $C_{41}H_{65}N_3O_{12}$ 791.5; found $[M + H]^+$ 792.9.

*6.6.7. 11,12-Carbonate 2′-O-acetyl-3-O-(n-pentyl)carbamoyl descladinosylazithromycin derivative (**4f**)*

White solid, yield 72%, mp 132–134 °C, TLC R_f = 0.7 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, CDCl3) δ 5.24 (s, 1H), 4.90–4.83 (s, 2H), 2.19 (s, 4H), 2.05 (s, 4H), 1.93 (s, 1H), 1.80 (s, 1H), 1.69 (s, 1H), 1.47 (s, 4H), 1.31 (d, *J* = 1.0 Hz, 5H), 1.25 (s, 8H), 1.19–1.18 (m, 3H), 1.07 (s, 5H), 0.90 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 181.43, 174.69, 155.95, 103.53, 99.74, 91.87, 86.34, 86.16, 85.83, 74.15, 73.48, 73.33, 70.58, 69.28, 65.97, 60.80, 60.65, 50.19, 43.66, 41.16, 40.34, 40.25, 38.46, 36.37, 29.91, 29.71, 29.00, 22.38, 22.34, 21.79, 21.19, 21.11, 20.99, 15.41, 14.99, 14.01, 12.32, 10.07, 9.65. MS (ESI) *m*/*z* calcd. for $C_{39}H_{69}N_3O_{12}$ 771.5; found $[M + H]^+$ 773.7.

*6.6.8. 11,12-Carbonate 2′-O-acetyl-3-O-(n-hexyl)carbamoyl descladinosylazithromycin derivative (**4g**)*

White solid, yield 67%, mp 131–133 °C, TLC R_f = 0.7 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, CDCl3) δ 4.91–4.83 (m, 2H), 3.71–3.68 (m, 1H), 3.50–3.47 (m, 1H), 3.28–3.26 (m, 1H), 2.75 (s, 2H), 2.66–2.58 (m, 4H), 2.37 (s, 2H), 2.19 (s, 2H), 2.10 (s, 1H), 2.03 (d, *J* = 8.1 Hz, 4H), 1.67 (s, 1H), 1.60 (s, 1H), 1.51 (s, 2H), 1.46 (s, 1H), 1.42 (s, 1H), 1.39 (s, 1H), 1.26 (s, 26H), 1.08 (s, 5H), 0.96 (s, 1H), 0.94 (s, 1H), 0.88 (s, 10H). HRMS (AP-ESI) *m*/*z* calcd for $C_{40}H_{71}N_3O_{12}$ 786.5034, found $[M + H]^+$ 786.5107.

*6.6.9. 11,12-Carbonate 2′-O-acetyl-3-O-(benzyl)N-methylcarbamoyl descladinosylazithromycin derivative (**4h**)*

Black solid, yield 43%, mp 121–123 °C, TLC R_f = 0.7 (CH_2Cl_2:MeOH = 10:1); MS (ESI) *m*/*z* calcd. for $C_{41}H_{65}N_3O_{12}$ 791.5; found $[M + H]^+$ 792.8.

*6.6.10. 3-O-(Phenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5a**)*

White solid, yield 53%, mp 118–120 °C, TLC R_f = 0.6 (CH2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.02 (m, 5H), 5.24–5.21 (m, 1H), 5.12–5.07 (m, 1H), 4.62 (s, 1H), 4.30–4.24 (m, 1H), 3.82 (s, 4H), 3.57 (s, 1H), 3.30–3.27 (m, 1H), 3.20–3.11 (m, 1H), 2.88–2.82 (m, 2H), 2.51 (s, 1H), 2.44 (s, 3H), 2.38–2.35 (m, 1H), 2.70 (s, 2H), 2.21 (s, 1H), 2.09 (s, 1H), 2.01 (s, 2H), 1.90–1.88 (m, 2H), 1.79 (s, 1H), 1.61 (s, 1H), 1.50 (s, 1H), 1.45–1.42 (m, 3H), 1.32–1.22 (m, 8H), 1.17–1.15 (m, 2H), 1.14 (s, 1H), 1.09–1.07 (m, 4H), 1.04 (s, 1H), 0.98–0.96 (m, 1H), 0.91–0.90 (m, 6H). MS (ESI) *m*/*z* calcd. for $C_{38}H_{61}N_3O_{11}$ 735.4; found $[M + H]^+$ 736.8.

*6.6.11. 3-O-(3-Methylphenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5b**)*

White solid, yield 57%, mp 110–112 °C, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.52 (m, 1H), 7.34 (s, 1H), 7.20–7.16 (m, 1H), 6.89–6.82 (m, 1H), 6.18 (s, 1H), 5.30–5.21 (m, 1H), 5.11–5.08 (s, 1H), 4.64–4.62 (m, 1H), 4.19–4.14 (m, 1H), 3.55 (s, 1H), 3.27–2.21 (m, 19H), 2.07–1.83 (m, 4H), 1.63–1.59 (m, 2H), 1.53–1.40 (m, 4H), 1.36–1.31 (m, 1H), 1.28–1.21 (m, 6H), 1.19–1.02 (m, 10H), 1.01–0.84 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.93, 174.13, 153.49, 153.08, 139.12, 138.14, 129.03, 123.98, 118.51, 114.98, 104.17, 86.43, 85.53, 84.80, 79.51, 75.83, 72.94, 70.68, 69.25, 68.16, 65.66, 61.89, 43.27, 42.17, 40.06, 35.82, 35.04, 28.31, 26.20, 25.86, 21.76, 21.53, 21.33, 20.98, 15.76, 13.47, 10.12, 9.45, 4.98. MS (ESI) *m*/*z* calcd. for $C_{39}H_{63}N_3O_{11}$ 749.9; found $[M + H]^+$ 750.6.

*6.6.12. 3-O-(2-Methylphenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5c**)*

White solid, yield 66%, mp 115–118 °C, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–6.98 (m, 4H), 5.11–5.09 (m, 1H), 4.70–4.64 (m, 1H), 4.12–4.11 (m, 1H), 3.61 (s, 1H), 3.26–3.15 (s, 2H), 2.96–2.84 (m, 2H), 2.40–2.04 (m, 19H), 1.96–1.81 (m, 3H), 1.62–1.50 (m, 2H), 1.44 (s, 2H), 1.26–1.24 (m, 6H), 1.19–1.04 (m, 12H), 0.96–0.89 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.11, 153.34, 136.04, 130.45, 130.22, 127.11, 126.62, 123.66, 121.43, 104.06, 86.45, 84.84, 79.76, 75.90, 72.99, 70.48, 69.55, 69.29, 68.16, 65.83, 61.91, 43.34, 42.28, 40.09, 36.90, 36.08, 34.94, 28.36, 26.14, 25.84, 21.83, 21.33, 21.02, 17.79, 15.71, 13.55, 10.12, 9.49, 5.04. MS (ESI) *m*/*z* calcd. for $C_{39}H_{63}N_3O_{11}$ 749.4; found $[M + H]^+$ 750.6.

*6.6.13. 3-O-(2-Fluorophenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5d**)*

White solid, yield 69%, mp 110–112 °C, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.01 (m, 4H), 5.38–4.93 (m, 4H), 4.49–4.14 (m, 2H), 3.82–3.71 (m, 1H), 3.56–2.82 (m, 4H), 2.42–1.89 (m, 14H), 1.80–1.44 (m, 7H), 1.33–1.10 (m, 10H), 1.11–0.81 (m, 13H). MS (ESI) *m*/*z* calcd. for $C_{38}H_{60}FN_3O_{11}$ 753.4; found $[M + H]^+$ 754.7.

*6.6.14. 3-O-(3-Methoxyphenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5e**)*

White solid, yield 60%, mp 111–113 °C, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.52 (m, 1H), 7.20–7.14 (m, 1H), 7.00–6.96 (m, 1H), 6.63–6.56 (m, 1H), 5.23–5.07 (m, 2H), 4.63–4.53 (m, 1H), 4.23–4.16 (m, 1H), 3.81 (s, 3H), 3.55 (m, 1H), 3.28–3.18 (m, 2H), 2.89–2.81 (m, 2H), 2.49–2.14 (m, 10H), 2.06–1.97 (m, 2H), 1.94–1.82 (m, 2H), 1.65–1.60 (m, 1H), 1.47–1.43 (m, 3H), 1.35–1.33 (m, 1H), 1.31–1.20 (m, 10H), 1.17–0.83 (m, 17H). MS (ESI) *m*/*z* calcd. for $C_{39}H_{63}N_3O_{12}$ 765.4; found $[M + H]^+$ 766.5.

*6.6.15. 3-O-(Benzyl)N-methylcarbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5f**)*

White solid, yield 55%, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, CDCl3) δ 7.513–7.510 (m, 2H), 7.51–7.10 (m, 5H), 5.69–5.66 (m, 1H), 5.09–5.06 (m, 1H), 4.72–4.69 (m, 2H), 4.03–4.01 (m, 1H), 3.61–3.58 (m, 1H), 3.18–3.12 (m, 1H), 2.88–2.83 (m, 2H), 2.36–2.35 (m, 1H), 2.26 (s, 4H), 2.21 (s, 4H), 2.20 (s, 1H), 2.09 (s, 3H), 2.08 (s, 1H), 1.51 (s, 1H), 1.49 (s, 1H), 1.43 (m, 3H), 1.26 (s, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 1.19–1.18 (m, 1H), 1.12 (s, 2H), 1.11 (s, 2H), 1.07 (s, 4H), 1.058–1.055 (m, 3H), 0.93–0.90 (m, 8H), 0.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.05, 160.36, 153.31, 139.41, 129.88, 110.00, 109.07, 103.81, 86.22, 84.85, 79.59, 75.72, 72.85, 70.45, 69.04, 68.23, 65.67, 61.99, 55.33, 43.15, 42.11, 39.99, 35.90, 35.09, 31.98, 29.65, 29.38, 28.44, 26.06, 25.85, 22.67, 21.75, 21.33, 20.97, 15.78, 14.15, 13.46, 10.12, 9.46, 4.96. MS (ESI) *m*/*z* calcd. for $C_{40}H_{65}N_3O_{11}$ 763.5; found $[M + H]^+$ 764.8.

*6.6.16. 3-O-(2-Chlorophenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5g**)*

White solid, yield 69%, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (400 MHz, CDCl3) δ 7.52–6.99 (m, 4H), 5.12–5.08 (m, 1H), 4.64 (s, 1H), 3.62 (s, 1H), 3.29–3.25 (s, 1H), 2.99–2.94 (s, 1H), 2.36–2.35 (m, 2H), 2.30–2.28 (m, 6H), 2.24–2.20 (m, 3H), 2.02–2.01 (m, 2H), 1.65–1.62 (m, 2H), 1.45–1.44 (m, 3H), 1.32 (s,

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1H), 1.31–1.30 (m, 1H), 1.26–1.24 (m, 16H), 1.16 (s, 1H), 1.14 (s, 1H), 1.09–1.06 (m, 4H), 0.93–0.88 (m, 7H). MS (ESI) *m/z* calcd. for $C_{36}H_{60}ClN_3O_{11}$ 769.4; found $[M + H]^+$ 770.6.

*6.6.17. 3-O-(3-Chlorophenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5h**)*

White solid, yield 72%, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, CDCl3) δ 7.81–7.01 (m, 4H), 5.10–5.08 (m, 1H), 4.62 (s, 1H), 4.22–4.13 (m, 1H), 3.59–3.51 (m, 1H), 3.29–3.19 (m, 2H), 2.86–2.81 (m, 2H), 2.39–2.21 (m, 11H), 2.10–1.83 (m, 5H), 1.68–1.61 (m, 1H), 1.49–1.41 (m, 3H), 1.36–1.18 (m, 11H), 1.15–1.05 (m, 9H), 0.92–0.83 (m, 7H). MS (ESI) *m/z* calcd. for $C_{36}H_{60}ClN_3O_{11}$ 769.4; found $[M + H]^+$ 770.6.

*6.6.18. 3-O-(4-Fluorophenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5i**)*

White solid, yield 66%, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, CDCl3) δ 8.14–6.90 (m, 4H), 5.13–4.98 (m, 1H), 4.54 (s, 1H), 4.17–4.16 (m, 1H), 3.48 (s, 1H), 3.24–3.19 (m, 1H), 2.77–2.65 (m, 2H), 2.40–2.10 (m, 10H), 1.99–1.92 (m, 2H), 1.54–1.50 (m, 2H), 1.35 (s, 2H), 1.18–1.10 (m, 19H), 1.05–0.99 (m, 7H), 0.85–0.78 (m, 7H). HRMS (AP-ESI) *m/z* calcd for $C_{38}H_{60}FN_3O_{11}$ $[M + H]^+$ 753.4212; found $[M + H]^+$ 754.4316.

*6.6.19. 3-O-(3-Fluorophenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5j**)*

White solid, yield 57%, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, CDCl3) δ 7.64–6.71 (m, 4H), 5.23–5.07 (m, 1H), 4.69–4.54 (m, 1H), 4.26–4.20 (m, 1H), 3.28–3.18 (m, 1H), 2.84–2.83 (m, 1H), 2.46–2.38 (m, 3H), 2.27–2.20 (m, 3H), 2.06–2.00 (m, 4H), 1.82–1.80 (m, 1H), 1.51–1.43 (m, 3H), 1.25 (s, 15H), 1.23 (s, 2H), 1.22 (s, 1H), 1.15–1.03 (m, 9H), 0.92–0.83 (m, 9H). HRMS (AP-ESI) *m/z* calcd for $C_{38}H_{60}FN_3O_{11}$ 753.4212; found $[M + H]^+$ 754.4274.

*6.6.20. 3-O-(3-Trifluoromethyl phenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5k**)*

White solid, yield 61%, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, CDCl3) δ 8.12–7.42 (m, 2H), 7.18–6.72 (m, 2H), 5.35–5.08 (m, 1H), 4.62–4.53 (m, 1H), 4.18–4.16 (m, 1H), 3.56–3.55 (m, 2H), 3.26–3.16 (m, 1H), 2.84–2.83 (m, 1H), 2.38–2.22 (m, 7H), 2.12–2.00 (m, 2H), 1.91–1.84 (m, 2H), 1.68–1.62 (m, 3H), 1.42–1.24 (m, 19H), 1.14–1.08 (m, 5H), 0.90 (s, 10H). MS (ESI) *m/z* calcd. for $C_{39}H_{60}F_3N_3O_{11}$ 803.4; found $[M + H]^+$ 804.7.

*6.6.21. 3-O-(4-Trifluoromethyl phenyl)carbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5l**)*

White solid, yield 70%, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, CDCl3) δ 7.83–7.54 (m, 4H), 5.08–5.05 (m, 1H), 4.60 (s, 1H), 3.56 (s, 2H), 3.55 (s, 2H), 2.58 (s, 2H), 2.35 (s, 1H), 2.27 (s, 2H), 2.20 (s, 1H), 1.64 (s, 1H), 1.45 (s, 1H), 1.41 (s, 3H), 1.39 (s, 1H), 1.37 (s, 2H), 1.35 (s, 1H), 1.33 (s, 1H), 1.32 (s, 2H), 1.29 (s, 8H), 1.26 (s, 1H), 1.20 (s, 1H), 1.14 (s, 1H), 1.13 (s, 1H), 1.08 (s, 1H), 1.07 (s, 1H), 1.06 (s, 1H), 1.04 (s, 1H), 0.92 (s, 2H), 0.90 (s, 8H), 0.88 (s, 3H). MS (ESI) *m/z* calcd. for $C_{39}H_{60}F_3N_3O_{11}$ 803.4; found $[M + H]^+$ 804.7.

*6.6.22. 3-O-(Phenyl)N-methylcarbamoyl descladinosylazithromycin 11,12-cyclic carbonate (**5m**)*

Black solid, yield 71%, mp 109–112 °C, TLC R_f = 0.6 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.52 (m, 1H), 7.37–7.32 (m, 3H), 7.21–7.11 (m, 1H), 5.12–4.78 (m, 2H), 4.36–4.29 (m, 1H), 4.23–4.17 (m, 1H), 3.76–3.67 (m, 1H), 3.35–3.25 (m, 4H), 2.91–2.81 (m, 2H), 2.40–2.31 (m, 5H), 2.23–2.20 (m, 1H), 2.13 (s, 1H), 2.07–2.02 (s, 2H), 1.95–1.92 (m, 2H), 1.76–1.68 (m, 2H), 1.47–1.41 (m, 2H), 1.33 (s, 1H), 1.29–1.18 (m, 16H), 1.08–1.01 (m, 4H), 0.98–0.83 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 154.72, 153.44, 130.96, 128.86, 104.98, 87.04, 76.00, 73.04, 70.26, 60.10, 37.15, 31.94, 31.45, 30.59, 30.47, 30.41, 30.38, 30.21, 29.71, 29.62, 29.37, 26.13, 25.84, 23.77, 22.99, 22.70, 22.47, 21.81, 21.39, 21.07, 21.03, 20.88, 15.85, 15.25, 14.12, 13.73, 10.08, 7.55. MS (ESI) *m/z* calcd. for $C_{39}H_{63}N_3O_{11}$ 749.4; found $[M + H]^+$ 750.6.

*6.6.23. 3-O-(4-Methylphenyl)carbamoyl-11-O-(benzyl)carbamoyl descladinosylazithromycin (**6a**)*

White solid, yield 45%, TLC R_f = 0.2 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.03 (m, 9H), 4.97–4.90 (m, 1H), 4.66–4.62 (m, 1H), 4.52–4.50 (m, 1H), 4.22–4.15 (m, 1H), 3.83 (s, 1H), 3.41–3.33 (m, 1H), 3.25–3.17 (m, 2H), 2.94–2.85 (m, 4H), 2.45–2.44 (m, 1H), 2.38 (s, 1H), 2.33 (s, 5H), 2.28 (m, 3H), 2.21 (m, 6H), 2.07–2.06 (m, 3H), 2.02–2.01 (m, 1H), 1.95–1.93 (m, 1H), 1.82–1.79 (m, 2H), 1.70–1.63 (m, 2H), 1.49–1.47 (m, 2H), 1.25–1.21 (m, 8H), 1.15 (s, 1H), 1.13 (s, 1H), 1.09–1.06 (m, 5H), 0.93–0.91 (m, 7H). MS (ESI) *m/z* calcd. for $C_{46}H_{72}N_4O_{11}$ 856.5; found $[M + H]^+$ 857.7.

*6.6.24. 3-O-(Phenyl)carbamoyl-11-O-(benzyl)carbamoyl descladinosylazithromycin (**6b**)*

White solid, yield 55%, TLC R_f = 0.2 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.02 (m, 10H), 5.23–5.20 (m, 1H), 5.09–5.07 (m, 1H), 4.76–4.62 (m, 1H), 4.31–4.25 (m, 1H), 3.95 (s, 1H), 3.64–3.58 (m, 1H), 3.27–3.13 (m, 5H), 2.84–2.82 (m, 2H), 2.442–2.440 (m, 1H), 2.38 (s, 4H), 2.27 (s, 2H), 2.21 (s, 1H), 2.09–2.02 (m, 2H), 1.77–1.72 (m, 1H), 1.608–1.606 (m, 1H), 1.45–1.42 (m, 3H), 1.26–1.22 (m, 15H), 1.14 (s, 3H), 1.07 (s, 5H), 0.90 (s, 7H). MS (ESI) *m/z* calcd. for $C_{45}H_{70}N_4O_{11}$ 842.5; found $[M + H]^+$ 843.6.

*6.6.25. 3-O-(Phenyl)carbamoyl-11-O-(n-hexyl)carbamoyl descladinosylazithromycin (**6c**)*

White solid, yield 55%, TLC R_f = 0.2 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.01 (m, 5H), 5.03–5.00 (m, 1H), 4.25–4.23 (m, 1H), 3.64–3.61 (m, 1H), 3.38–3.36 (m, 2H), 3.150–3.146 (m, 2H), 2.84–2.81 (m, 1H), 2.43–2.37 (m, 2H), 2.26 (s, 5H), 2.22 (s, 3H), 2.13–2.08 (m, 1H), 2.02–1.95 (m, 2H), 1.85–1.83 (m, 1H), 1.72–1.60 (m, 3H), 1.26 (s, 19H), 1.21 (s, 3H), 1.17 (s, 7H), 1.08–1.07 (m, 3H), 0.99 (s, 3H), 0.88 (s, 9H). MS (ESI) *m/z* calcd. for $C_{44}H_{76}N_4O_{11}$ 836.6; found $[M + H]^+$ 838.8.

*6.6.26. 3-O-(3-Methylphenyl)carbamoyl-11-O-(4-methylbenzyl) carbamoyl descladinosylazithromycin (**6d**)*

White solid, yield 41%, TLC R_f = 0.2 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.14 (m, 8H), 5.21–5.08 (m, 1H), 4.80–4.72 (m, 2H), 4.65–4.59 (m, 1H), 4.47–4.38 (m, 1H), 4.18–4.16 (m, 1H), 3.89 (s, 1H), 3.66–3.48 (m, 2H), 3.28–3.13 (m, 2H), 2.99–2.74 (m, 2H), 2.53–2.45 (m, 1H), 2.42–2.37 (m, 4H), 2.33–2.32 (m, 9H), 2.29–2.27 (m, 4H), 2.24–2.14 (m, 2H), 2.08–1.98 (m, 2H), 1.93–1.79 (m, 2H), 1.65–1.59 (m, 2H), 1.53–1.42 (m, 2H), 1.35–1.19 (m, 8H), 1.16–0.97 (m, 9H), 0.94–0.84 (m, 6H). HRMS (AP-ESI) *m/z* calcd for $C_{47}H_{74}N_4O_{11}$ 870.5354, found $[M + H]^+$ 871.5370.

*6.6.27. 3-O-(3-Methylphenyl)carbamoyl-11-O-(4-methoxylbenzyl) carbamoyl descladinosylazithromycin (**6e**)*

White solid, yield 39%, TLC R_f = 0.2 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–6.79 (m, 8H), 5.13–4.92 (m, 1H), 4.71–4.56 (m, 1H), 4.34–4.18 (m, 3H), 3.97 (s, 1H), 3.77–3.71 (m, 4H), 3.58–3.50 (m, 1H), 3.40 (s, 2H), 3.22–3.14 (m, 1H), 2.89 (s, 1H), 2.81 (s, 1H), 2.38–2.09 (m, 12H), 1.97 (s, 2H), 1.83 (s, 1H), 1.36 (s, 1H), 1.18–0.96 (m, 22H), 0.81 (s, 7H), 0.60–0.59 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 161.68, 160.95, 159.78, 158.66, 158.60, 138.24, 132.23, 130.87, 130.09, 129.99, 129.53, 129.40, 129.11, 128.92, 126.74,

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123.58, 118.97, 115.88, 114.51, 114.37, 114.18, 114.01, 63.85, 60.18, 55.73, 55.63, 55.48, 42.22, 40.66, 40.58, 40.37, 40.16, 39.96, 39.54, 39.33, 31.76, 29.50, 29.22, 29.18, 29.06, 22.57, 21.96, 21.94, 21.72, 21.24, 14.41, 14.10, 10.99. HRMS (AP-ESI) *m/z* calcd for $C_{47}H_{74}N_4O_{12}$ 886.5303, found $[M + H]^+$ 887.5386.

*6.6.28. 3-O-(3-Methylphenyl)carbamoyl-11-O-(2-chlorobenzyl) carbamoyl descladinosylazithromycin (**6f**)*

White solid, yield 42%, TLC $R_f = 0.2$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.71 (m, 3H), 7.55–7.52 (m, 4H), 7.18–7.16 (m, 1H), 4.32–4.29 (m, 7H), 2.83–2.81 (m, 7H), 2.33 (s, 2H), 1.76–1.65 (m, 7H), 1.49–1.49 (m, 10H), 1.29–1.25 (m, 13H), 0.98–0.94 (m, 12H), 0.90–0.86 (m, 3H). HRMS (AP-ESI) *m/z* calcd for $C_{46}H_{71}ClN_4O_{11}$ 890.4808, found $[M + H]^+$ 891.4893.

*6.6.29. 3-O-(2-Methylphenyl)carbamoyl-11-O-(benzyl)carbamoyl descladinosylazithromycin (**6g**)*

White solid, yield 48%, TLC $R_f = 0.2$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.70 (m, 1H), 7.55–7.52 (m, 1H), 7.38–7.32 (m, 4H), 7.20–7.14 (m, 2H), 7.05–6.99 (m, 1H), 4.39–4.37 (m, 1H), 4.26–4.14 (m, 2H), 3.69–3.14 (m, 1H), 2.68 (s, 4H), 2.61–2.60 (m, 1H), 2.452–2.446 (m, 1H), 2.33 (s, 3H), 2.04–2.02 (s, 2H), 1.70–1.65 (m, 1H), 1.45–1.44 (m, 1H), 1.43 (s, 1H), 1.41 (s, 1H), 1.39 (s, 1H), 1.33 (s, 2H), 1.32 (s, 1H), 1.30 (s, 1H), 1.29–1.8 (m, 6H), 1.25 (s, 15H), 1.18 (s, 4H), 1.04 (s, 2H), 0.94–0.92 (m, 2H), 0.902–0.896 (m, 3H), 0.88 (s, 3H), 0.86 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{46}H_{72}N_4O_{11}$ 856.5198, found $[M + H]^+$ 857.5291.

*6.6.30. 3-O-(4-Methoxylphenyl)carbamoyl-11-O-(n-hexyl) carbamoyl descladinosylazithromycin (**6h**)*

White solid, yield 33%, TLC $R_f = 0.2$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–6.57 (m, 4H), 4.26–4.20 (m, 1H), 3.80 (s, 4H), 3.59–3.55 (m, 1H), 3.49 (s, 1H), 3.21–3.18 (m, 2H), 3.14–3.08 (m, 1H), 3.01–2.97 (m, 3H), 2.72–2.63 (m, 6H), 1.82–1.69 (m, 5H), 1.44–1.43 (m, 1H), 1.42 (s, 1H), 1.40 (s, 1H), 1.31–1.28 (m, 16H), 1.25 (s, 11H), 0.94 (s, 1H), 0.88–0.83 (m, 16H). HRMS (AP-ESI) *m/z* calcd for $C_{45}H_{78}N_4O_{12}$ 866.5616, found $[M + H]^+$ 867.5670.

*6.6.31. 3-O-(4-Chlorophenyl)carbamoyl-11-O-(benzyl)carbamoyl descladinosylazithromycin (**6i**)*

White solid, yield 30%, TLC $R_f = 0.2$ (CH_2Cl_2:MeOH = 10:1); HRMS (AP-ESI) *m/z* calcd for $C_{45}H_{69}ClN_4O_{11}$ 876.4651, found $[M + H]^+$ 877.4705.

*6.6.32. 11,12-Cyclic carbonate 2′-O-acylimidazolide descladinosylazithromycin derivative (**7**)*

White solid, yield 21%, mp 148–150 °C, TLC $R_f = 0.6$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24–8.22 (m, 1H), 7.53–6.38 (m, 3H), 5.69–5.66 (m, 1H), 5.10–5.06 (m, 1H), 4.71–4.48 (m, 2H), 4.03–3.87 (m, 1H), 3.70–3.49 (m, 1H), 3.20–3.13 (m, 1H), 2.88–2.61 (m, 2H), 2.39–2.31 (m, 2H), 2.27–2.26 (m, 3H), 2.20–2.16 (m, 6H), 2.09–2.04 (m, 4H), 1.89–1.85 (m, 1H), 1.63–1.58 (m, 1H), 1.49 (s, 1H), 1.44–1.40 (m, 3H), 1.29–1.17 (m, 8H), 1.13–1.10 (m, 3H), 1.08–1.06 (m, 6H), 0.97–0.86 (m, 7H). MS (ESI) *m/z* calcd. for $C_{35}H_{58}N_4O_{11}$ 710.4; found $[M + H]^+$ 711.6.

*6.6.33. 11,12-Cyclic carbonate 2′-O-(phenyl)carbamoyl descladinosylazithromycin derivative (**8a**)*

White solid, yield 71%, mp 115–118 °C, TLC $R_f = 0.75$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.04 (m, 5H), 5.27–5.09 (m, 2H), 4.63 (s, 1H), 4.12–4.10 (m, 1H), 3.60–3.56 (m, 1H), 3.23–3.21 (m, 1H), 2.92–2.84 (m, 2H), 2.39–2.36 (m, 1H), 2.28–2.16 (m, 11H), 2.06–2.00 (m, 2H), 1.91–1.84 (m, 3H), 1.62 (s, 1H), 1.44 (s, 3H), 1.38–1.32 (m, 2H), 1.26 (s, 7H), 1.16–1.14 (m, 3H), 1.10–1.08 (m, 6H), 0.92–0.91 (m, 6H). MS (ESI) *m/z* calcd. for $C_{38}H_{61}N_3O_{11}$ 735.4; found $[M + H]^+$ 736.4.

*6.6.34. 11,12-Cyclic carbonate 2′-O-(2-methylphenyl)carbamoyl descladinosylazithromycin derivative (**8b**)*

White solid, yield 64%, mp 114–116 °C, TLC $R_f = 0.75$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–6.98 (m, 4H), 5.12–5.08 (m, 1H), 4.70–4.59 (m, 1H), 4.14–4.12 (m, 1H), 3.61 (s, 1H), 3.25–3.18 (m, 2H), 2.97–2.84 (m, 2H), 2.40–2.27 (m, 6H), 2.24–2.22 (m, 2H), 2.17–2.15 (m, 5H), 2.08–2.04 (m, 1H), 1.95–1.92 (m, 1H), 1.87–1.81 (m, 1H), 1.67–1.58 (m, 2H), 1.44–1.40 (m, 3H), 1.37–1.24 (m, 10H), 1.19–1.02 (m, 11H), 0.96–0.84 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.09, 156.15, 153.51, 136.07, 130.44, 127.18, 123.72, 86.46, 84.89, 79.70, 76.50, 75.87, 72.97, 70.48, 69.33, 68.16, 65.78, 61.92, 57.97, 52.40, 43.35, 42.26, 40.08, 36.04, 35.91, 34.95, 30.65, 28.27, 26.13, 25.85, 21.81, 21.34, 21.06, 17.80, 17.36, 15.73, 13.54, 10.13, 9.47, 6.65, 5.03. HRMS (AP-ESI) *m/z* calcd for $C_{39}H_{63}N_3O_{11}$ $[M + H]^+$ 749.4463, found $[M + H]^+$ 750.4575.

*6.6.35. 11,12-Cyclic carbonate 2′-O-(3-methylphenyl)carbamoyl descladinosylazithromycin derivative (**8c**)*

White solid, yield 60%, mp 110–112 °C, TLC $R_f = 0.75$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.02 (m, 4H), 4.65–4.46 (m, 1H), 4.15–4.13 (m, 1H), 3.84–3.70 (m, 1H), 3.56–3.50 (m, 1H), 3.24–3.20 (m, 2H), 2.88–2.85 (m, 1H), 2.38–2.33 (m, 5H), 2.26 (s, 10H), 2.22 (s, 2H), 2.16–2.13 (m, 3H), 2.07–2.01 (m, 3H), 1.63–1.59 (m, 2H), 1.48–1.43 (m, 2H), 1.26 (s, 14H), 1.15–1.14 (m, 1H), 1.11–1.07 (m, 3H), 0.92–0.89 (m, 6H). MS (ESI) *m/z* calcd. for $C_{39}H_{63}N_3O_{11}$ 749.4; found $[M + H]^+$ 750.6.

*6.6.36. 11,12-Cyclic carbonate 2′-O-(3-methoxylphenyl)carbamoyl descladinosylazithromycin derivative (**8d**)*

White solid, yield 68%,TLC $R_f = 0.75$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–6.97 (m, 4H), 4.83–4.71 (m, 2H), 3.72–3.59 (m, 3H), 3.35–3.34 (m, 1H), 2.70–2.64 (m, 2H), 2.53–2.50 (m, 1H), 2.40–2.30 (m, 10H), 2.14 (s, 1H), 2.07–2.06 (m, 4H), 1.92–1.89 (m, 2H), 1.33–1.32 (m, 1H), 1.30–1.23 (m, 13H), 1.14–1.12 (m, 3H), 1.07–1.06 (m, 5H), 0.92–0.88 (m, 10H). HRMS (AP-ESI) *m/z* calcd for $C_{39}H_{63}N_3O_{12}$ 765.4412, found $[M + H]^+$ 766.4465.

*6.6.37. 11,12-Cyclic carbonate 2′-O-(3-chlorophenyl)carbamoyl descladinosylazithromycin derivative (**8e**)*

White solid, yield 62%, mp 113–115 °C, TLC $R_f = 0.75$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.00 (m, 4H), 5.01–4.95 (m, 1H), 4.80–4.73 (m, 1H), 4.54–4.45 (m, 1H), 3.93–3.88 (m, 1H), 3.70–3.69 (m 1H), 3.60–3.55 (m, 2H), 3.11–3.03 (m, 4H), 2.92–2.90 (m, 1H), 2.82–2.79 (m, 3H), 2.70–2.69 (m, 1H), 2.57–2.53 (m, 1H), 2.35–2.30 (m, 1H), 2.17–2.13 (m, 1H), 2.03–2.00 (m, 1H), 1.91–1.89 (m, 1H), 1.60–1.59 (m, 3H), 1.54 (s, 1H), 1.47–1.46 (m, 3H), 1.43–1.41 (m, 3H), 1.37–1.35 (m, 3H), 1.25–1.24 (m, 11H), 1.22 (s, 2H), 1.20 (s, 1H), 1.01–0.98 (m, 3H), 0.92–0.88 (m, 4H). HRMS (AP-ESI) *m/z* calcd for $C_{38}H_{60}ClN_3O_{11}$ 769.3916, found $[M + H]^+$ 770.3960.

*6.6.38. 11,12-Cyclic carbonate 2′-O-(4-fluorophenyl)carbamoyl descladinosylazithromycin derivative (**8f**)*

White solid, yield 68%, TLC Rf = 0.75 (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.37 (m, 2H), 7.24–6.98 (m, 2H), 5.24–5.08 (m, 1H), 4.70–4.47 (m, 2H), 4.26–4.13 (m, 1H), 3.93–3.82 (m, 2H), 3.49–3.21 (m, 1H), 2.90–2.80 (m, 1H), 2.38–2.35 (m, 1H), 2.32–2.14 (m, 8H), 2.11–2.00 (m, 3H), 1.92–1.76 (m, 3H), 1.68 (s, 1H), 1.53–1.48 (m, 2H), 1.43 (s, 2H), 1.37–1.17 (m, 14H), 1.13–1.07 (m, 5H), 0.97–0.83 (m, 8H). MS (ESI) *m/z* calcd. for $C_{38}H_{60}FN_3O_{11}$ 753.4; found $[M + H]^+$ 754.9.

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*6.6.39. 11,12-Cyclic carbonate 2′-O-(3-fluorophenyl)carbamoyl descladinosylazithromycin derivative (**8g**)*

White solid, yield 66%, TLC $R_f = 0.75$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03–6.67 (m, 4H), 5.18–5.02 (m, 1H), 4.62–4.42 (m, 1H), 4.25–4.08 (m, 3H), 3.79 (s, 1H), 3.60–3.42 (m, 1H), 2.80–2.74 (m, 1H), 2.31–2.12 (m, 7H), 1.97–1.92 (m, 3H), 1.61 (s, 1H), 1.53–1.49 (m, 3H), 1.36 (s, 2H), 1.18 (s, 18H), 1.05–1.00 (m, 4H), 0.88–0.84 (m, 9H). MS (ESI) *m/z* calcd. for $C_{38}H_{60}FN_3O_{11}$ 753.4; found $[M + H]^+$ 754.8.

*6.6.40. 11,12-Cyclic carbonate 2′-O-(4-butylphenyl)carbamoyl descladinosylazithromycin derivative (**8h**)*

White solid, yield 56%, TLC $R_f = 0.75$ (CH_2Cl_2:MeOH = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–6.99 (m, 4H), 5.24–5.08 (m, 1H), 4.69–4.51 (m, 1H), 4.32–4.20 (m, 1H), 3.88 (s, 1H), 2.89–2.53 (m, 2H), 2.39–2.20 (m, 3H), 2.02–1.99 (m, 2H), 1.74–1.68 (m, 3H), 1.65–1.58 (m, 4H), 1.54–1.52 (m, 1H), 1.43 (s, 2H), 1.30–1.22 (m, 26H), 1.14–1.13 (m, 2H), 1.10–1.07 (m, 2H), 1.04–1.00 (m, 1H), 0.98–0.81 (m, 11H), 0.77–0.69 (m, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{42}H_{69}N_3O_{11}$ 791.4932, found $[M + H]^+$ 792.4992.

Conflict of interest

The authors declare that this study was carried out only with public funding. There is no funding or no agreement with commercial for profit firms.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.10.065.

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