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Design, synthesis and antibacterial evaluation of novel C-11, C-9 or C-2′-substituted 3-*O*-descladinosyl-3-ketoclarithromycin derivatives

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ABSTRACT

A novel series of 3-*O*-descladinosyl-3-keto-clarithromycin derivatives, including 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives and 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives, were designed, synthesized and evaluated for their *in vitro* antibacterial activity. Among them, some derivatives were found to have activity against resistant bacteria strains. In particular, compound **9b** showed not only the most significantly improved activity (16 μg/mL) against *S. aureus* ATCC43300 and *S. aureus* ATCC31007, which was >16-fold more active than that of CAM and AZM, but also the best activity against *S. pneumoniae* B1 and *S. pyogenes* R1, with MIC values of 32 and 32 μg/mL. In addition, compounds **9a**, **9c**, **9d** and **9g** exhibited the most effective activity against *S. pneumoniae* AB11 with MIC values of 32 or 64 μg/mL as well. Unfortunately, 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives failed to exhibit better antibacterial activity than references. It can be seen that the combined modification of the C-3 and C-11 positions of clarithromycin is beneficial to improve activity against resistant bacteria, while the single modification of the C-2′' position is very detrimental to antibacterial activity.

Macrolide antibiotics are lipophilic compounds with a lactone ring structure, which are produced by *Streptomyces*[1] and show broad antibacterial spectrum and excellent antibacterial activity. They has also good pharmacokinetic properties, such as high oral bioavailability, good plasma stability and long half-life, etc. Macrolides antibiotics are widely used in the treatment of various respiratory infectious diseases, such as respiratory and urinary diseases caused by Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* due to their strong antibacterial activity *in vivo* and *in vitro*, low toxicity and high safety. At present, they have become one of the most widely used antibiotics in the world.

Macrolides promote the dissociation of peptidyl tRNA on ribosome, inhibit the extension of peptide chain, and block the synthesis of bacterial protein, thereby producing antibacterial effect by binding to the entry of peptide exit channel of peptidyl transferase center on 23S rRNA of 50S subunit of bacterial ribosome.[2] Erythromycin (Fig. 1) is the representative drug of the first generation of macrolide antibiotics,[3,4] and was approved by FDA in 1952 to treat respiratory tract infection, sexually transmitted diseases, skin and soft tissue infection.[5,6] However, erythromycin is subjected to the intramolecular condensation of C-6 hydroxyl and C-9 carbonyl groups under the catalysis of gastric acid to generate 6,9-dehydration metabolites, and then 6,9,12-dehydrated metabolites by intramolecular condensation with C-12 hydroxyl group,[7] which reduce the bioavailability of erythromycin and produce gastrointestinal side effects. Consequently, this greatly limits the widespread use of erythromycin clinically. Clarithromycin (CAM) and azithromycin (AZM) are two representative drugs of the second generation macrolide antibiotics and overcome the shortcoming of poor pharmacokinetic properties of erythromycin *in vivo*,[7] which were approved by FDA in 1991. They were prepared from erythromycin as the starting material through 6 and 4 steps of chemical reactions, respectively. Compared with erythromycin, they show significantly enhanced antibacterial activity and greatly improved pharmacokinetic properties.[8]

Unfortunately, the prevalence of drug-resistant bacteria appears rapidly due to the abuse of antibiotics, whcih weakens the effectiveness of macrolides.[9,10] The bacterial resistance to macrolides are mainly caused by the methylation of A2058 in 23S rRNA nucleotide of bacterial ribosome by methyltransferase encoded by the *erm* gene.[11,12] This methylation effect can block the formation of hydrogen bonds between the C-2′ hydroxyl group in macrolides and nucleotide residue A2058,

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thereby greatly reducing the binding force between them. On the other hand, the efflux pump protein encoded by the *mef* gene on bacterial cell membrane can recognize macrolides and expel them out of bacterial cells,[13] which reduces the accumulation of drugs in bacterial cell and puts them below the effective concentration. This also leads to bacterial resistance. Therefore, it is urgent to develop new macrolide antibiotics against resistant bacteria.

The results of X-ray eutectic structure show that 3-*O*-cladinose of macrolide antibiotics is not necessary for antibacterial activity, and the C-3 position modification can enhance the activity against resistant bacteria.[14] Consequently, the third generation macrolide antibiotics represented by telithromycin, cethromycin and solithromycin (Fig. 2) have been designed and synthesized to respond to bacterial resistance. Compared with the previous two generations of macrolides, this generation of macrolides is highly active to erythromycin-resistant pathogens. For example, telithromycin[15] was approved by FDA in 2004 to treat chronic bronchitis, pharyngitis and community acquired pneumonia. It has a strong inhibitory effect on erythromycin resistant *Streptococcus pneumoniae* and *Haemophilus influenzae*. As a promising clinical candidate drug, cethromycin[16] and solithromycin[17] are considered to be effective drugs in the treatment of community acquired pneumonia caused by MLS_B resistant bacteria, and display prominent inhibitory effect on *Staphylococcus* and *Enterococci* as well as macrolides resistant respiratory pathogens. The common structural features of these drugs are the C-3 keto group and arylalkyl side chains on their skeleton.

Our previous[18–20] studies showed that the combined modification of the C-3 and C-11 positions of CAM could significantly improve activity against resistant bacteria and retain activity against sensitive bacteria. On this basis, we designed and synthesized a series of novel 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives in order to overcome the *erm* gene or the *mef* gene-mediated bacterial resistance and expand antibacterial specturm. On the one hand, the removal of C-3 position cladinose can suppress the active efflux of bacteria. On the other hand, 11-*O*-carbamoyl side chain is favorable to combine with A752 through hydrogen bond, π-π stacking or van der waals interaction, so as to improve anti-resistant activity. Furthermore, we previously[21] opened the 14-membered lactone ring of CAM by oxidation reaction, and reconstructed the new 15-membered lactone ring by esterification reaction, whose stereo conformation changed to some extent to facilitate binding with bacterial ribosome. Its 2′-OH can combine with the A2058 and A2059 of ribosome of sensitive bacteria through hydrogen bonding to exhibit anti-sensitive bacteria activity.[22] However, the highly methylated A2058 residue of ribosome of resistant bacteria cannot serve as an H-bond donor to participate in coordination of the water molecule on bacterial ribosome,[23] thereby exerting activity against resistant bacteria. Thus, it is a feasible method that introduction of new aryl side chains into 2′-OH to establish strong binding force with new binding site in the ribosome of resistant bacteria. For the purpose of improving the activity of compounds against resistant bacteria, we designed and synthesized 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives by modifying the C-2′ and C-9 positions of CAM. We hoped that the aryl side chains introduced at the C-2′ and C-9 positions of CAM could produce an additional binding force with U790 in domain II of 23S rRNA of ribosome of resistant bacteria, and eventually improved anti-resistant bacteria activity.[24]

The synthetic method for 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives is shown in Scheme 1. CAM as the starting material was treated with 36% hydrochloric acid to generate 3-descladinosylclarithromycin **2**.[25] Then, the reaction of **2** with acetic anhydride catalyzed by triethylamine gave acetyl product **3**,[26] which subsequently reacted with bis(triehloromethyl)carbonate (BTC) to afford the 11,12-cyclic carbonate **4** in the presence of pyridine.[27] After that, **4** was converted into 3-ketone product **5** under pyridinium chlorochromate (PCC) oxidation,[28] which was treated with alkanolamine at 15 °C to give key intermediate 2′-*O*-acetyl-11-*O*-(aminoethyl)carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin **6a-6b**. The terminal hydroxyl group on the C-11 side chain of **6a-6b** was esterified with methanesulfonyl chloride (MsCl) to obtain mesylate intermediate **7a-7b**. Intermediate **7a-7b** was treated with sodium azide (NaN_3) in the mixed solvent of water and N,*N*-dimethylformamide (DMF) at 60 °C to produce key intermediate **8a-8b**. After that, the click reaction of **8a-8b** with the corresponding phenylacetylene catalyzed by cuprous iodide (CuI) in toluene solution[9] and subsequent deprotection in methanol (MeOH)[29] afford target compounds **9a-9g**. Their structures were confirmed by ^{1}H NMR and MS spectra.

The synthetic method for 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives (19a**–19t**) is shown in Scheme 2. The C-9 carbonyl group of CAM was reduced with sodium borohydride to obtain the intermediate **10**. The hydroxyl groups on the C-4′', C-2′ and C-9-positions of the intermediate **10** reacted with TESCl to give TES protected product **11**. Subsequently, the hydroxyl groups on the C-11 and C-12 positions were subjected to oxidative cracking and ring opening by treating selectively with $Pb(OAc)_4$ to obtain the key intermediate **12**, which was further treated with ethanolamine to produce the secondary amine **13** through the first reductive amination reaction.[30] The secondary amine of **13** and 37% HCHO undergo a second reductive amination reaction to obtain tertiary amine product **14**.[30] We prepared crude tertiary amine **14** through a three-step reaction from **11** using the "one-pot method" due to the instability of **12**. Under the catalysis of LiOH, **14** was hydrolyzed to afford the carboxylic acid **15**, which was further purified by column chromatography to give its pure product. The intramolecular esterification of **15** completed the cyclization process to obtain cyclization product **16**.[31] The TES protecting groups on the C-2′ and C-9 positions, and cladinose on the C-3 position were removed from **16** to give **17** under dilute hydrochloric acid.[25] The condensation of **17** with various substituted benzoyl chloride gave condensation products **18a-18t**,[32] whose hydroxyl groups at the C-3 position were further oxidized by Dess-Martin periodinane to produce the target compounds **19a-19t**. Their structures were confirmed by ^{1}H NMR and MS spectra.

The *in vitro* antibacterial activity of target compounds were determined by the standard broth microdilution procedures recommended by NCCLS. The tested strains included three susceptible strains of *S. aureus* ATCC25923 (erythromycin-susceptible strain), *Bacillus subtilis* ATCC9372 (penicillin-susceptible strain) and *Pseudomonas aeruginosa*

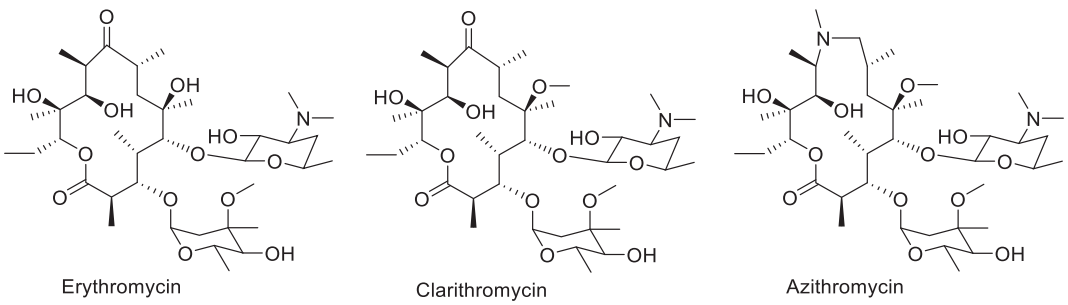


Fig. 1. Structures of erythromycin, clarithromycin and azithromycin.

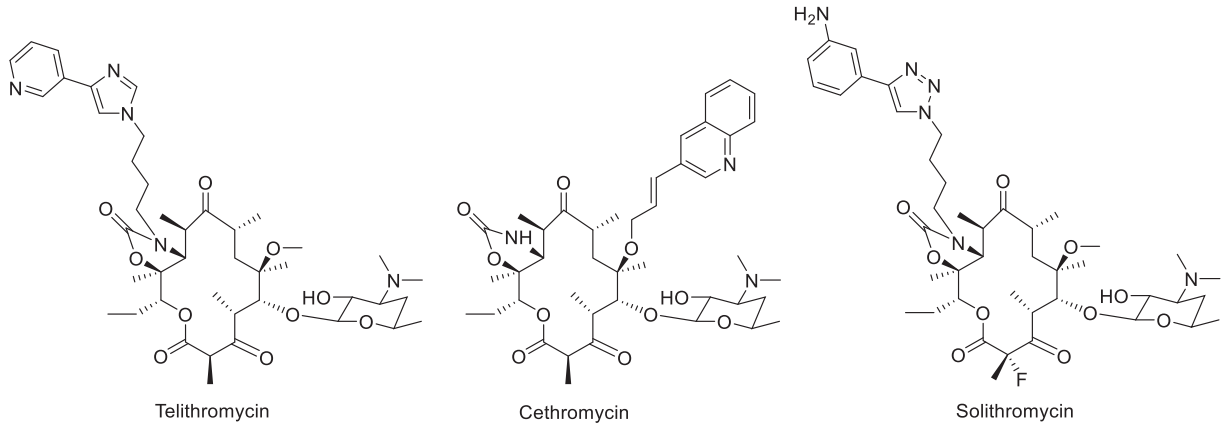
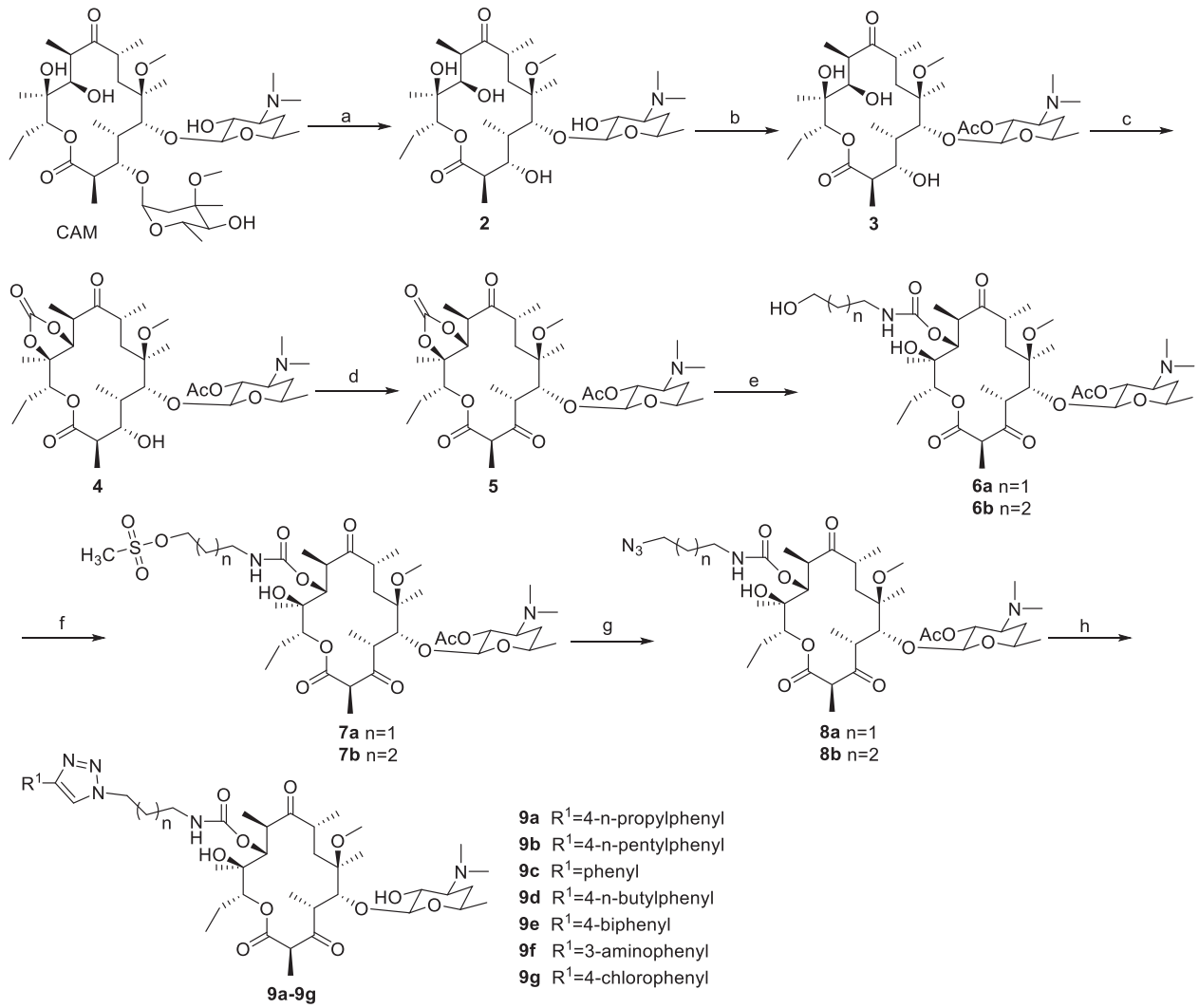
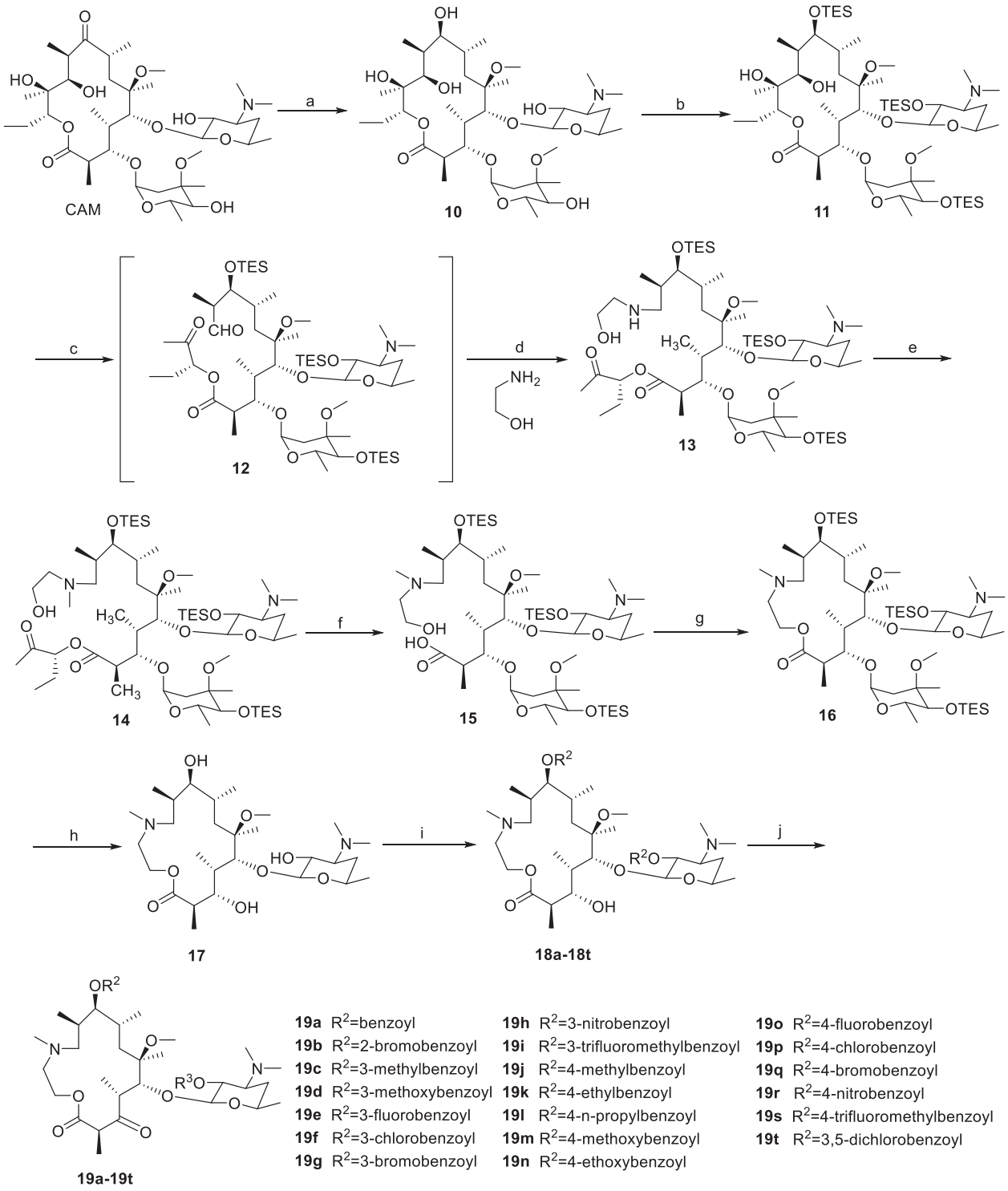


Fig. 2. Structures of telithromycin, cethromycin and solithromycin.



Scheme 1. Synthesis of 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives (9a–9 g). Reagents and conditions: (a) HCl, H_2O, rt, 5 h, 83%; (b) Ac_2O, Et_3N, DCM, 0 °C ~ rt, 36 h, 94%; (c) pyridine, BTC, DCM, 0 °C ~ rt, 20 h, 99%; (d) PCC, DCM, rt, 24 h, 88%; (e) 3-aminopropanol/4-amino-1-butanol, pyridine hydrochloride, 15 °C, 2 h, 39 ~ 42%; (f) MsCl, Et_3N, DCM, 0 ~ 25 °C, 2 h, 88 ~ 89%; (g) NaN_3, DMF, H_2O, 60 °C, 12 h, 72 ~ 78%; (h) i) phenylacetylene, CuI, toluene, 90 °C, 24 h; ii) CH_3OH, 55 °C, 24 h, 55 ~ 60%.

ATCC27853 (penicillin-susceptible strain), and five resistant strains of *S. aureus* ATCC43300 (methicillin-resistant strain), *S. aureus* ATCC31007 (penicillin-resistant strain), *S. pyogenes* R1 (erythromycin-resistant strain isolated clinically), *S. pneumoniae* B1 (erythromycin-resistant strain expressing the *erm*B gene) and *S. pneumoniae* AB11 (erythromycin-resistant strain expressing the *erm*B and *mef*A genes). The minimal inhibitory concentration (MIC) values for the above target compounds as well as CAM and AZM as the references were tested



Scheme 2. Synthesis of 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin (19a–19 t). Regents and conditions: (a) $NaBH_4$, CH_3OH-THF, rt, 24 h, 52%; (b) TESCl, imidazole, DMF, 0 °C to rt, 18 h, 68%; (c) $Pb(OAc)_4$, $CHCl_3$, 0 °C, 0.5 h; (d) ethanolamine, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (e) 37% HCHO, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (f) LiOH, THF-C_2H_5OH-H_2O, rt, 6 h, 30% in four steps from intermediate 11; (g) i) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, THF, rt, 4 h; ii) DMAP, CH_3CN, reflux, 0.5 h, 51%; (h) 1 M HCl, EtOH, 60 °C, 2 h, 77%; (i) Substituted benzoyl chloride, DCM, Et_3N, 0 °C to rt, 4 h; (j) Dess-Martin periodinane, DCM, rt, 2 h, 15 ~ 53% in two steps from intermediate 17.

against a panel of sensitive and resistant bacteria strains, which are presented in Table 1.

Compared to the references CAM and AZM, 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives **9a-9g** universally showed greatly improved activity against *S. pneumoniae* B1, *S. pneumoniae* AB11, *S. pyogenes* R1, *S. aureus* ATCC43300 and *S. aureus* ATCC31007, but weak activity against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372. Unfortunately, none of them displayed better antibacterial activity against *P. aeruginosa* ATCC27853 than AZM (MIC = 32 μg/mL[33]). Among them, **9b** showed significantly improved activity (16 μg/mL) against *S. aureus* ATCC43300 and *S. aureus* ATCC31007, which was >16-fold more active than that of CAM and AZM (>256 and

Table 1
In vitro antibacterial activity of 3-*O*-descladinosyl-3-keto-clarithromycin derivatives.

Minimum inhibitory concentration/ MIC (μg/mL)								
Compounds	*S. aureus* ATCC43300[a]	*S. aureus* ATCC31007[b]	*S. pneumoniae* B1[c]	*S. pneumoniae* AB11[d]	*S. pyogenes* R1[e]	*P. aeruginosa* ATCC27853[f]	*S. aureus* ATCC25923[g]	*B. Subtilis* ATCC9372[h]
9a	256	256	64	32	64	128	16	4
9b	16	16	32	32	32	128	32	16
9c	> 256	> 256	256	64	256	> 128	32	4
9d	64	64	64	32	64	> 128	64	4
9e	128	256	128	64	64	> 128	64	16
9f	> 256	> 256	256	128	256	> 128	64	32
9g	> 256	> 256	256	32	256	> 128	64	16
19a	>256	>256	>256	>256	>256	>128	128	>128
19b	>256	>256	>256	>256	>256	>128	128	>128
19c	>256	>256	>256	>256	>256	>128	128	>128
19d	>256	>256	>256	>256	>256	>128	128	>128
19e	>256	>256	>256	>256	>256	>128	128	>128
19f	>256	>256	>256	>256	>256	>128	64	>128
19g	>256	>256	>256	>256	>256	>128	64	>128
19h	>256	>256	>256	>256	>256	>128	128	>128
19i	>256	>256	>256	>256	>256	>128	128	>128
19j	>256	>256	>256	>256	>256	>128	128	>128
19k	>256	>256	>256	>256	>256	>128	64	>128
19l	>256	>256	>256	>256	>256	>128	64	>128
19m	>256	>256	>256	>256	>256	>128	64	>128
19n	>256	>256	>256	>256	>256	>128	128	>128
19o	>256	>256	>256	>256	>256	>128	128	>128
19p	>256	>256	128	>256	>256	>128	128	>128
19q	>256	>256	>256	>256	>256	>128	128	>128
19r	>256	>256	>256	>256	>256	>128	64	>128
19s	>256	>256	>256	>256	>256	>128	64	>128
19t	>256	>256	>256	>256	>256	>128	128	>128
CAM	>256	>256	>256	256	256	16	≤0.25	≤0.25
AZM	>256	>256	>256	128	256	32	≤0.25	≤0.25

[a] *S. aureus* ATCC43300: methicillin-resistant strain;
[b] *S. aureus* ATCC 31007: penicillin-resistant strain;
[c] *S. pneumoniae* B1: erythromycin-resistant strain expressing the *erm*B gene;
[d] *S. pneumoniae* AB11: erythromycin-resistant strain expressing the *erm*B and *mef*A genes;
[e] *S. pyogenes*: erythromycin-resistant strain isolated clinically;
[f] *P. aeruginosa* ATCC27853: penicillin-susceptible strain, not characterized;
[g] *S. aureus* ATCC25923: erythromycin-susceptible strain;
[h] *B. Subtilis* ATCC9372; penicillin-susceptible strain.

>256 μg/mL), while **9a**, **9c**, **9d** and **9g** exhibited the most effective activity against *S. pneumoniae* AB11 with MIC values of 32 or 64 μg/mL, showing 2 or 4-fold better than CAM (128 μg/mL) and 4 or 8-fold better than AZM (256 μg/mL), respectively. In the inhibition of *S. pneumoniae* AB11, the most active compound **9b** exhibited an MIC value of 32 mg/mL, >8-fold better than CAM and AZM (>256 μg/mL). In addition, **9b** displayed the best activity with MIC value of 32 μg/mL against *S. pyogenes* R1, 8-fold better than CAM and AZM (256 and 256 μg/mL). Unfortunately, 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives **19a-19t** failed to exhibit better antibacterial activity than references.

In general, the 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives **9a-9g** exhibited improved activity against resistant bacteria and weak activity against susceptible bacteria in comparison with CAM and AZM. Furthermore, some target compounds showed favorable activity against Gram-positive bacteria but weak activity against Gram-negative bacteria, probably because they were difficult to pass through the cell wall of Gram-negative bacteria. The above results indicate that simultaneous modification of the C-3 and C-11 positions of CAM can enhance activity against resistant bacterial strains and partially retain activity against sensitive bacterial strains. We believe that the C-11 side chain may directly interact with the nucleotide A752. Especially, the alteration of the length and the different substituents on the terminal benzene ring of the C-11 side chain lead to the change of interaction force, thereby influencing antibacterial activity for the target compounds. Actually, the alkyl substitution on the terminal benzene ring is more beneficial to increasing antibacterial activity of the target compounds such as **9a**, **9b** and **9d**. It is possible that the flexible alkyl side chain is able to adapt to the binding pocket of bacterial ribosomes and produce new forces. In contrast, 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives **19a-19t** did not show effective bacteriostatic effect. This series display poor activity against three susceptible bacteria because their C-2′ ester side chains cannot bind to A2058 and A2059, leading to a decrease antibacterial activity. Similarly, this series also exhibited poor activity against five resistant bacteria. The possible reasons were that introduction of the C-9 aryl side chain changed the conformation of this series to a certain extent compared with CAM, resulting in the inability to bind to the U790 of bacterial ribosome closely. Moreover, the C-2′ or C-9 aryl side chain was short and lacked flexibility, which could not reach U790 and bind to it.

In order to study the chemical stability of 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives, **19a, 19i, 19j** and **19p** were selected and determined in a phosphate solution (pH = 7.4) at 25 °C by HPLC method. The result indicated that the peak areas of these compounds were almost unchanged within 24 h, which confirmed that the above tested compounds had excellent chemical stability.[34,35]

In summary, we designed and synthesized a series of novel 3-*O*-descladinosyl-3-keto-clarithromycin derivatives, including 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives and 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives, and evaluated their *in vitro* antibacterial activity. The results indicated that 11-*O*-carbamoyl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives had activity against resistant bacteria strains. Among them, **9b** showed not only the most significantly improved activity (16 μg/mL) against

S. aureus ATCC43300 and *S. aureus* ATCC31007, which was > 16-fold more active than CAM and AZM (>256 and > 256 μg/mL), but also the best activity against *S. pneumoniae* B1 and *S. pyogenes* R1, with MIC values of 32 and 32 μg/mL, which were >8 and >8-fold stronger than that of CAM and AZM (256 and 256 μg/mL), respectively. In addition, **9a**, **9c**, **9d** and **9g** exhibited the most effective activity against *S. pneumoniae* AB11 with MIC values of 32 or 64 μg/mL, showing 2 or 4-fold better than CAM (128 μg/mL) and 4 or 8-fold more better than AZM (256 μg/mL), respectively. Unfortunately, 2′,9(S)-diaryl-3-*O*-descladinosyl-3-keto-clarithromycin derivatives failed to display more potent antibacterial activity than references. It can be seen that the combined modification of the C-3 and C-11 positions is beneficial to improve activity against resistant bacteria, while the modification of the single C-2″ position is very detrimental to antibacterial activity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.128110.

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