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Design, synthesis and antibacterial evaluation of novel 15-membered 11a-azahomoclarithromycin derivatives with the 1, 2, 3-triazole side chain

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ABSTRACT

Macrolides are widely prescribed in clinic to treat various respiratory tract infections. However, due to their inappropriate use, the prevalence of macrolide-resistant strains among clinical isolates has become a concern for public health. Therefore, novel macrolides skeleton structures against resistant pathogens are badly needed. Thus, three series of novel 15-membered 11a-azahomoclarithromycin derivatives (the series A-C) with the 1, 2, 3-triazole side chain were designed and synthesized through creatively opening the ring of clarithromycin (CAM), expanding the ring properly and introducing a suitable side chain of 1, 2, 3-triazole at the C12 and C13 positions, and evaluated for their antibacterial activity. The antibacterial results indicated that compounds **38b**, **38l** and **38v** possessed strong antibacterial activity against *Staphylococcus aureus* ATCC25923 (0.25 μg/mL) and *Bacillus subtilis* ATCC9372 (0.25 μg/mL). Furthermore, compounds **9e** and **38g** were found to exhibit promising potent activity (8 μg/mL) against *Streptococcus pneumonia* AB11 expressing the *erm*B and *mef*A genes. In addition, the determination of minimum bactericidal concentration (MBC) indicated that the most promising compounds **38b**, **38l**, **38v**, **9e** and **38g** were excellent bacteriostatic agents. The bactericidal curve showed that **9e** exhibited antibacterial activity through bacteriostatic mechanism. Finally, **38b**, **38l** and **38v** were confirmed to be non-toxic to MCF-7 breast cancer cells up to a concentration of 32 μg/mL in preliminary cytotoxicity assay. In summary, **38b**, **38l**, **38v**, **9e** and **38g** can be served as lead compounds to provide a new perspective for further structural optimization.

Keywords: macrolide antibiotics, antibacterial activity, resistant bacterial strains, structure-activity relationships

1. Introduction

Macrolides [1, 2] (**Fig. 1**) are widely used in the treatment of respiratory tract infections because of their potent activity, low toxicity and high safety. Since the first macrolide antibiotic erythromycin A was discovered, the development of macrolide antibiotics has gone through three generations. Erythromycin A, as the first generation macrolide antibiotic, was found from a Philippine soil sample in 1949 [3]. It is effective for various infections, including skin and soft tissue infections, sexually transmitted diseases and respiratory tract infections, but its clinical use is relatively limited due to its bioavailability and gastrointestinal side effects [4]. Therefore, it is urgent to study a new generation of macrolide antibiotics with excellent pharmacokinetic properties. Clarithromycin (CAM) [5, 6] and azithromycin (AZM) [7] launched in 1991, which belong to the second generation macrolide antibiotics. Their pharmacokinetic properties are more significantly improved than that of erythromycin A, including broader antibacterial spectrum, higher intracellular concentration, longer half-life and higher bioavailability of oral administration [8, 9]. However, some bacterial strains have gradually become resistant strains to the second generation macrolide antibiotics. Their mechanism of drug resistance mainly includes two kinds of ribosomal methylation (mediated by *erm* methyltransferase) and efflux pump (mediated by *mef*-gene) [10-12]. Those leads to new generation of macrolide scaffolds that are badly needed [13]. Therefore, the third generation macrolides: telithromycin [14], cethromycin [15] and solithromycin [16, 17] have been rapidly developed, which belong to ketolides derivatives. Telithromycin, for example, is the first ketolide macrolide approved by the US FDA in 2004 for mainly treating infections such as chronic bronchitis, pharyngitis and community-acquired pneumonia (CAP) [18]. Besides, cethromycin and solithromycin as promising clinical candidates, are known to be effective for the treatment of CAP caused by macrolide-lincosamide-streptogramin B (MLS_B) resistant bacteria. Compared with the previous two generations of macrolides, the third generation of macrolides are extremely effective against erythromycin-resistant pathogens [14, 15, 19]. For example, telithromycin showed strong activity against erythromycin-resistant *Streptococcus pneumoniae* and *Haemophilus influenza*, cethromycin exhibited excellent potency against macrolide-resistant respiratory tract pathogens and solithromycin

exhibited promising activity against *Staphylococcus* and *Enterococcus spp*. They share common structural characteristics, such as a 3-ketone group and an aryl alkyl side chain. In particular, the aryl alkyl side chains play an important role in generating anti-resistant bacteria activity because the aryl alkyl side chains allow the drugs to bind tightly to bacterial ribosomes [20-25]. Although the third generation macrolides have excellent antimicrobial activity, researchers have been still making great efforts to modify the structure of macrolides to overcome the problems of bacterial resistance. Ian B. Seiple1 et al [26] designed and sythesized some 14-membered and 15-membered azaketolide derivatives by replacing the C3-cladinose residue of CAM by a ketone group, introducing a nitrogen atom and some active triazole side chains into the macrocycle. The azaketolide derivatives with various macrocyclic scaffolds exhibited extremely strong activity against erythromycin-resistant strains.

<Insert **Fig. 1**>

It has been reported that in order to seek newer macrolides with novel structural skeletons, the C13 position of erythromycin A was modified by chemical biosynthesis [27, 28]. The resulting C13 derivatives enhanced the antibacterial activity against drug-resistant strains, which indicated that the C13 position of erythromycin A plays an important role in combating the drug-resistant strains. However, the number of the C13 derivatives that were obtained by chemical biosynthesis did not meet the research needs due to the lack of reactivity of the C13 position. In view of this, Tomoaki Miura et al [29] established a relevant macrolactone skeleton reconstruction methodology by chemical synthesis. Subsequently, Tomohiro Sugimoto et al [30] reported a related macrolactone skeleton reconstruction method using CAM as raw material.

The above described methodologies and feasible synthetic methods give us some inspiration, which also prompted our new research. Therefore, our design strategy is outlined as follows (**Fig. 2**). The C-C bond between the C11 and C12 positions of CAM was oxidatively cleaved, an active triazole side was inserted into the resulting macrolactone skeleton, and macrolactonization of the acyclic skeleton produced the desired novel 15-membered 11a-azahomoclarithromycin derivatives with an active triazole side chains at the C12 and C13 positions, one type of side chains substituted at C12 position giving series B, and the other type of side chains substituted at C13 position affording series

A and C. The above two types of side chains were expected to be spatially close and combine with the new bacterial ribosomal base U790, which may generate hydrogen bond interaction, π-π stacking interaction, electrostatic interaction and hydrophobic interaction [20, 31]. Thus, we designed series A, B and C based on the following ideas. Firstly, the main group 2'-OH was retained to interact with A2058 and A2059 in domain V of 23S rRNA, producing strong antibacterial activity against susceptible bacteria [32]. Secondly, the stereo conformation of CAM skeleton was changed to form favorable conformation to increase the binding force to bacterial ribosomes. Spatially, some groups on the 11a-azahomoclarithromycin skeleton approach and bind to new nucleotide binding sites in domain V of 23S rRNA to give additional binding forces. These changes in stereochemistry are to enhance the antibacterial activity against drug-resistant bacteria. Finally, the introduced side chains with appropriate length, flexibility and extension direction in space were easily to interact with the U790 of 23S rRNA [20, 31].

<Insert **Fig. 2**>

2. Chemistry

2.1. Synthesis of 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin derivatives (Series A)

The 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin **9a-l** (Series A) as the C-13 substituted derivatives, the synthetic route of which is shown in **Scheme 1**. CAM **1** was treated with sodium borohydride to give the 9(S)-dihydro-clarithromycin **2** [33], and subsequent selective protection of 9, 2', 4"-hydroxyl groups of **2** by triethylchlorosilane provided 11, 12-diol **3** [34]. **3** was oxidized by lead tetraacetate to afford an acyclic aldehyde intermediate **4**. The intermediate **6a-l** was obtained from **4** in 2 steps: (1) reductive amination [35] of **4** with various substituted aminoalcohols **5a-l** gave the secondary amine; (2) methylation of the intermediate secondary amine at the 11-a with formaldehyde. **6a-l** was successfully prepared in "one-pot" method from **3** due to the instability of **4** and the resulting secondary amine. However, due to many byproducts produced during the preparation **6a-l**, led to the purification of **6a-l** was difficult. Consequently, only the crude intermediate **6a-l** could be obtained by column chromatography. Saponification of **6a-l** formed

carboxylic acid **7a-l**, which was followed macrolactonization [36] to give the desired 15-membered macrolides **8a-l**. Finally, **9a-l** (series A) were successfully prepared by deprotection of the silane groups from **8a-l** by using hydrogen fluoride-pyridine. In summary, the synthesis of **9a-l** involves two procedures: ring opening procedure (from starting materials **1** to intermediate **4**) and cyclization procedure (from intermediate **4** to target compounds **9a-l**).

<Insert **Scheme 1**>

The synthetic route of the key intermediates **5a-l** is shown in **Scheme 2**. Under weak acid conditions, R-epichlorohydrin **10** was stereoselectively ring-opened with sodium azide to yield an azide intermediate **11** [37]. Subsequently, **11** was treated with a variety of substituted phenylacetylene **12** in the presence of L-ascorbic acid sodium salt and copper sulfate to form chloroethanol **13** [38]. Cyclization reaction of **13** with sodium hydroxide solution gave epoxy **14**, which was stereoselectively ring-opened with aqueous ammonia to provide various substituted aminoalcohols **5a**, **5c**, **5e**, **5g**, **5i** and **5k**. Followed as the general procedure described above, the other corresponding enantiomers **5b**, **5d**, **5f**, **5h**, **5j** and **5l** were also prepared from S-epichlorohydrin **15** as raw starting material. The two groups of synthesized intermediates consist of **5a-l**.

<Insert **Scheme 2**>

2.2. Synthesis of 15-membered 11a-aza-12-(1, 2, 3-triazoles)homoclarithromycin derivatives (Series B)

The 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin **23a-l** (series B) as the C-12 substituted derivatives, the synthetic route of which is shown in **Scheme 3**. The target compounds **23a-l** (series B) were prepared from **4** by application of the same cyclization procedure as **9a-l** (series A).

<Insert **Scheme 3**>

The synthetic route of intermediates **19a-l** is shown in **Scheme 4**. The azide **26** was given from Boc-L-serine methyl ester **24** in 2 steps: (1) mesylation of **24** with methanesulfonyl chloride formed the mesylate; (2) azidation of the resulting mesylate with sodium azide. Subsequently, **26** was treated with various substituted phenylacetylene **12** in the presence of L-ascorbic acid sodium salt and copper sulfate to produce ester **27**. Then **27** was reduced by sodium borohydride [39] to yield alcohol **28**, which was followed deprotection of the Boc group from **28** using hydrochloric acid to give the various substituted aminoalcohols **19a**, **19c**, **19e**, **19g**, **19i** and **19k**. According to the general procedure, the other corresponding enantiomers **19b**, **19d**, **19f**, **19h**, **19j** and **19l** were also given from Boc-D-serine methyl ester **29** as raw starting material. The two groups of synthesized intermediates consist of **19a-l**.

<Insert **Scheme 4**>

2.3. Synthesis of 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin derivatives (Series C)

The 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin **38a-v** (series C) as the C-13 substituted derivatives, the synthetic route of which is shown in **Scheme 5**. The target compounds **38a-v** (series C) were prepared from **4** by application of the same cyclization procedure as **9a-l** (series A).

<Insert **Scheme 5**>

Furthermore, the synthetic route of intermediates **34a-v** is shown in **Scheme 6**. Diazotization of **39** with sodium nitrite under acidic conditions, and then treatment with sodium azide formed the azide **40**. Subsequently, **40** was reacted with methyl propiolate **41** in the presence of L-ascorbic acid sodium salt and copper sulfate to obtain ester **42**. **42** was subjected to reduction reaction with lithium aluminum hydride to give alcohol **43**, which then was treated with phosphorus tribromide [40] to yield bromine **44**. Introduction of epoxy moiety (R)-glycidol **45** to bromine **44** was achieved to produce the epoxy **46** by utilizing the intermolecular nucleophilic substitution reaction [41]. **46** was

stereoselectively ring-opened with aqueous ammonia to give various substituted aminoalcohols **34a**, **34c**, **34e**, **34g**, **34i**, **34k**, **34m**, **34o**, **34q**, **34s** and **34u** as side chains [34]. The other corresponding enantiomers **34b**, **34d**, **34f**, **34h**, **34j**, **34l**, **34n**, **34p**, **34r**, **34t** and **34v** were provided by using the general procedure described above. The two groups of synthesized intermediates consist of **34a-v**. However, we failed to synthesize 2-azidopyridine **40** according to the synthetic procedure when **39** was 2-aminopyridine (**Scheme 7**). Therefore, **40** was prepared by another feasible synthetic method. The 2-hydrazinopyridine **49** was subjected to azidation with tert-butyl nitrite to generate **40** on the scale of 200 mg [42]. The corresponding substituted ethanolamine **34k** and **34l** were prepared from **40** according to the above synthetic procedure (**Scheme 6**).

<Insert **Scheme 6**>

<Insert **Scheme 7**>

2.4. Analysis and determination of the absolute configuration of compounds

By two consecutive reductive ammoniation, hydrolysis, cyclization and deprotection, the compounds in series A, B and C were synthesized from **4** and **5a-l**, **4** and **19a-l**, **4** and **34a-v**, respectively. None of the above reaction processes involved the cleavage and formation of chemical bonds linking the chiral carbon (C12 or C13). Therefore, the stereo configurations of C12 or C13 in the compounds are determined by the configurations of the **5a-l**, **19a-l**, and **34a-v**. The intermediates **5a-l** and **34a-v** belong to 1-substituted ethanolamines, and **19a-l** belong to 2-substituted ethanolamines. Finally, the representative intermediates **5a**, **5b**, **19a** and **19b** were selected to determine their stereo configurations using Mosher method [43, 44] and circular dichroism spectrum.

2.4.1. Analysis and determination of the absolute configuration of intermediates by Mosher method

According to the Mosher method reported in literatures [43, 44], the absolute configurations of intermediate **5a** possessing a secondary alcohol moiety were clarified by measuring the NMR spectra of their methoxy(trifluoromethyl)-phenylacetic (MTPA) esters. **5a** was reacted with (S)-(+)-MTPA chloride in the presence of pyridine to yield (S)-MTPA ester **50**. Meanwhile, the (R)-MTPA ester **51**

was also prepared according to this same synthetic method. Based on the ^{1}H NMR spectral data of MTPA esters (**50** and **51**), the chemical shift values were assigned to each other and the Δδ values (Δδ = Δδs – $\Delta\delta_R$) were calculated by Mosher method (**Table 1**). The results show $\Delta\delta_3 > 0$ and $\Delta\delta_2 > 0$, but $\Delta\delta_3 > 0$ has no reference because of the protons (**H3**) are affected by the nearest Mosher amide. Finally, the stereochemistry of **5a** was finally determined to be S-configuration.

<Insert **Table 1**>

2.4.2. Analysis and determination of the absolute configuration of intermediates by circular dichroism (CD) spectrum

The commercially available materials N-Boc-L-serine methyl ester **24** and N-Boc-D-serine methyl ester **29** are a pair of enantiomers, and their CD spectra show a mirror symmetry relationship. **24** and **29** were used as control, the CD spectra data of **5a**, **5b**, **19a** and **19b** were analyzed. Consequently, their configurations were determined to be S-, R-, S-, and R-configurations, respectively (**Fig. 3**). Here, we can clearly see that the conclusion about the configuration of **5a** is the same by using Mosher method and circular dichroism spectrum.

<Insert Fig. 3>

Based on the above analysis, the configuration of C13 in compound **9a** should be S-configuration, while those of other chiral carbons remain unchanged. Similarly, the configurations of C12 or C13 in other compounds were determined using the same method as that of **9a**.

3. Results and discussion

3.1. In vitro antibacterial activity of 11a-azahomoclarithromycin derivatives

The in vitro antibacterial activity of the 15-membered 11a-azahomoclarithromycin derivatives with 1, 2, 3-triazoles were evaluated against various sensitive and resistant bacterial strains. All the tested bacterial strains include *Staphylococcus aureus* ATCC25923 (erythromycin-susceptible strain), *Streptococcus pyogenes* 1 (erythromycin-susceptible strain isolated clinically), *Escherichia coli* ATCC25922 (penicillin-susceptible strain), *Pseudomonas aeruginosa* ATCC27853

(penicillin-susceptible strain, not characterized), *Bacillus subtilis* ATCC9372 (penicillin-susceptible strain), *Staphylococcus aureus* ATCC31007 (penicillin-resistant strain), *Staphylococcus aureus* ATCC43300 (methicillin-resistant strain), *Streptococcus pneumonia* B1 (erythromycin-resistant strain expressing the *erm*B gene), *Streptococcus pneumoniae* AB11 (erythromycin-resistant strain expressing the *erm*B and *mef*A genes) and *Streptococcus pyogenes* 2 (erythromycin-resistant strain isolated clinically). In all the above assays, AZM and CAM were used as controls. Determination of the in vitro antibacterial activity by minimum inhibitory concentration (MIC) was conducted using the broth microdilution method according to the Clinical and Laboratory Standards Institute guidelines [45].

3.1.1. In vitro antibacterial activity of the series A (9a-9l)

The antibacterial activity of the series A is showed in **Table 2**. The MIC results indicated that **9a**, **9b**, **9f**, **9h** and **9i** had better activity against *S. aureus* ATCC25923, *S. pyogenes* 1 and *B. subtilis* ATCC9372 than the others in the series A. Among them, **9i** exhibited the best activity against the three tested bacterial strains of *S. aureus* ATCC25923, *S. pyogenes* 1 and *B. subtilis* ATCC9372 with 0.5, 0.25 and 0.5 μg/mL, respectively. Besides, **9e** showed stronger activity against the tested resistant strains than CAM, exhibiting 16-32 fold increase in antibacterial activity against *S. aureus* ATCC31007, *S. aureus* ATCC43300, *S. pneumoniae* AB11 and *S. pyogenes* 2. In series A, **9e** had the strongest antibacterial activity against all the resistant bacteria, and its activity was well balanced.

<Insert **Table 2**>

Based on the above MIC data, the structure-activity relationships (SARs) of the series A against susceptible bacteria are summarized as follows. In series A, **9a** exhibited excellent antibacterial activity, but **9c-9l** showed a slight decrease in the antibacterial activity. This shows that the antibacterial activity of compounds without substituents on the phenyl group of the 1, 2, 3-triazole is stronger than those of the compounds with substituents. We infer that the introduction of substituent can affect the stereo structure of 11a-azahomoclarithromycin skeleton binding to bacterial ribosomes, thus weakening the binding ability of 2'-OH to A2058 and A2059 in domain V of 23S rRNA [32].

Therefore, the antibacterial activity of **9a** is stronger than that of **9c-9l**. However, **9i** exhibited excellent activity against sensitive bacteria. It is well known that the introduction of F atom can improve the liposolubility of compounds, which may explain why **9i** has excellent activity. Besides, the antibacterial activity of **9a** and **9b** is similar, which indicates that when the same substituent is on the phenyl group, its extension direction in space has little effect on the antibacterial activity. Similarly, **9c** and **9d**, **9i** and **9j** also conform to the above SARs.

On the other hand, the SARs of the series A against resistant bacteria are summarized as follows. Introduction of a long-chain aliphatic alkyl (4 carbon atoms) into the phenyl group of **9e** and **9f** showed extremely significantly improved activity against the resistant bacteria. However, introduction of the other substituents into the phenyl group of **9a**-**9d** and **9g**-**9l** did not increase significantly activity against the resistant bacteria. This indicates that the length of the aliphatic alkyl on the phenyl group has important effect on the antibacterial activity. The length of the aliphatic alkyl is too short (less than 3 atoms) has a negative impact on the antibacterial activity. It is possible that the 1, 2, 3-triazole side chain with appropriate length and flexibility more easily generates the π-π stacking interaction, electrostatic interaction and hydrophobic interaction with the U790 of 23S rRNA [20, 31]. So, **9e** and **9f** generate additional binding force with new binding site U790, thereby leading to stronger antibacterial activity. The antibacterial activity of **9e** is slightly stronger than that of **9f**, which indicates that the 1, 2, 3-triazole side chain with **S**-configuration is better than that with **R**-configuration in the antibacterial activity. In series A, **9i** and **9j**, **9k** and **9l** have the same SARs as **9e** and **9f**. The results indicate that the extension direction of 1, 2, 3-triazole side chains in space possesses some effect on the antibacterial activity.

3.1.2. In vitro antibacterial activity of the series B (23a-23l)

The antibacterial activity of the series B is showed in **Table 3**. Compared with CAM, the series B almost lose their activity against most susceptible bacteria. However, **23e**, **23f** and **23l** showed stronger activity against the tested resistant strains than CAM, especially **23e** exhibiting 8-16-fold increase in activity against *S. aureus* ATCC31007, *S. pneumonia* AB11 and *S. pyogenes* 2. **23e** had relatively balanced antibacterial activity against *S. aureus* ATCC31007 (16 μg/mL), *S. pneumonia* AB11 (16 μg/mL) and *S. pyogenes* 2 (16 μg/mL).

<Insert **Table 3**>

We systematically summarized the SARs of series B. **23e** displayed significantly improved activity against *S. aureus* ATCC31007, *S. pneumonia* AB11 and *S. pyogenes* 2, much better than the others in the series B. It suggests that introduction of a long-chain aliphatic alkane (4 carbon atoms) into the phenyl group can enhance the antibacterial activity compared with other substituents in the series B. We infer that the long-chain aliphatic alkane with 4 carbon atoms can make the 1, 2, 3-triazole side chain more easily to combine with the binding site U790 of 23S rRNA through the π-π stacking interaction, electrostatic interaction and hydrophobic interaction [20, 31]. Consequently, the additional binding ability to bacterial ribosomes of drug-resistant bacteria greatly improve in antibacterial activity. Besides, the MIC values of **23a** and **23b** are basically equal, which indicates that the stretching direction of the 1, 2, 3-triazole side chain in space do not affect the antibacterial activity against resistant bacteria. In series B, **23c** and **23d**, **23i** and **23j** have the similar SARs to **23a** and **23b**.

3.1.3. In vitro antibacterial activity of the series C (38a-38v)

The antibacterial activity of the series C is showed in **Table 4**. In Series C, **38b**, **38l** and **38v** displayed the stronger activity against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372 than the others with the MIC values 0.25 μg/mL, better than or equal to CAM. Moreover, the antibacterial activity of **38d** and **38f** against most susceptible bacteria was comparable to that of CAM, but they exhibited excellent antibacterial activity against *B. subtilis* ATCC9372 with an MIC value of 0.25 μg/mL.

On the other hand, **38g** and **38i** had not only significantly improved activity against all the resistant bacteria, showing 8-16-fold more potent antibacterial activity than CAM, but also extremely balanced antibacterial activity against the drug-resistant bacteria with the MIC values of 8-32 μg/mL. Besides, **38e**, **38j**, **38o**, **38q** and **38s** exhibited slightly stronger anti-resistant antibacterial activity with MIC values of 32-64 μg/mL than CAM.

<Insert **Table 4**>

The SARs of the series C against susceptible bacteria are shown below. **38b** exhibits stronger antibacterial activity against *S. aureus* ATCC25923, *S. pyogenes* 1, *P. aeruginosa* ATCC27853, *B. subtilis* ATCC9372 and *E. coli* ATCC25922 than that of **38a**, and the ratio (MIC_S/MIC_R) of which is 2 ~ 8. It shows that the 1, 2, 3-triazole side chain with **R**-configuration is better than that with **S**-configuration in the antibacterial activity. In series C, **38c** and **38d**, **38e** and **38f**, **38g** and **38h**, **38i** and **38j**, **38k** and **38l**, **38m** and **38n**, **38o** and **38p**, **38u** and **38v** possess the same SARs as **38a** and **38b**. Obviously, we can draw the conclusion that the extension direction of the 1, 2, 3-triazoles side chain in space has a significant effect on the antibacterial activity. In particular, the **R**-configuration side chain probably has more favorable conformation to interact with bacterial ribosomes than the **S**-configuration side chain, which may explain that compounds with the **R**-configuration side chains are stronger than compounds with **S**-configuration side chains in the antibacterial activity.

The SARs of the series C against resistant bacteria are also summarized as below. The antibacterial activity of **38c**, **38e**, **38g** and **38i** increases with the extension of the aliphatic alkane group, which demonstrates that the length of the introduced aliphatic alkane group on the phenyl group is closely related to its activity. Specially, the aliphatic alkane group in compound **38g** is 3 carbon atoms, which leads to the strongest antibacterial activity. This may be because the aliphatic alkane group with 3 carbon atoms produces stronger binding force with the binding site U790 than the others [20, 31]. Besides, the conformations of the 1, 2, 3-triazole side chains also have a certain influence on the antibacterial activity. **38e** exhibits more potent antibacterial activity against resistant bacteria than that of **38f**, which demonstrates that the **S**-configuration side chain is better than the **R**-configuration side chain in the antibacterial activity. **38g** and **38h**, **38i** and **38j**, **38o** and **38p**, **38q** and **38r**, **38s** and **38t** have also similar SARs as described above.

In general, the series A and series C belong to the C-13 substituted derivatives, possessing the 1, 2, 3-triazole side chains with one atom and three atoms between the 1, 2, 3-triazole and the 11a-azahomoclarithromycin skeleton, respectively. While the series B belongs to the C-12 substituted derivatives, possessing the 1, 2, 3-triazole side chains with one atom between the 1, 2, 3-triazole and the 11a-azahomoclarithromycin skeleton. As for the antibacterial activity against susceptible bacteria, the order of antibacterial activity of the three series is the series C > the series A > the series B. The results show that the compounds with the 1, 2, 3-triazole side chains at the C-13 position exhibit stronger activity than those with the 1, 2, 3-triazole side chains at the C-12 position. In addition, the

length between the 1, 2, 3-triazole and the 11a-azahomoclarithromycin skeleton has a positive effect on the antibacterial activity against susceptible bacteria. On the other hand, most of the derivatives in the series A and B exerted similar activity against resistant bacteria, while only **9e** and **9f** (the C-13 substituted derivatives) are much stronger activity against *S. aureus* ATCC43300 and *S. pneumoniae* B1 than **23e** and **23f** (the C-12 substituted derivatives). As for the series A and C, their antibacterial activity is similar, which shows clearly that the length between the 1, 2, 3-triazole and the 11a-azahomoclarithromycin skeleton does not have much effect on the antibacterial activity against resistant bacteria.

3.2. Bactericidal or bacteriostatic action

To confirmed whether the above promising compounds were bactericidal or bacteriostatic, we determined the minimal bactericidal concentration (MBC) values of **38b**, **38l** and **38v** against susceptible bacteria (*S. aureus* ATCC25923), and **9e** and **38g** against resistant bacteria (*S. pneumoniae* AB11) (**Table 5**). The results indicate that **38b**, **38l** and **38v** have all the MBC/MIC values of more than or equal to 512, exhibiting bacteriostatic action against *S. aureus* ATCC25923. In contrast, **9e** and **38g** have all the MBC/MIC values of 8, showing bacteriostatic behavior against *S. pneumoniae* AB11. The above results demonstrate that the tested compounds against sensitive and resistant bacterial strains are essentially achieved through bacteriostatic action.

<Insert **Table 5**>

3.3. Kinetics of the bactericidal activity

In order to further study and clarify the sterilization of the promising compounds in each time period, **9e** with certain bactericidal activity was chose to determine its time-bactericidal curve (**Fig. 4**). The results indicate that at the concentrations of 1, 2 and 4 MIC, **9e** exhibits certain bactericidal effect (0-9 h) and excellent bacteriostatic effect (9-24 h) against *S. pneumoniae* AB11, respectively. Thus, **9e** have a concentration-dependent inhibition on bacterial production, which also demonstrate that it is an excellent bacteriostatic agent from the microscopic point of view.

<Insert **Fig. 4**>

3.4. Cytotoxic evaluation on mammalian cells

38b, **38l** and **38v** with the MIC values of 0.25~0.5 μg/mL against most susceptible bacteria (such as *S. aureus* ATCC25923, *S. pyogenes* 1 and *B. subtilis* ATCC 9372) were selected to evaluate their cytotoxicity on MCF-7 breast cancer cells using 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (**Fig. 5**). The results show that **38l** has non-toxic to MCF-7 breast cancer cells up to a concentration of 32 μg/mL, while **38b** and **38v** are slight toxic. After incubation at a concentration of 64 or 128 μg/mL for 24 h, the tested cells percent viable is approximately 60%, which indicate that **38b**, **38l** and **38v** have moderate toxicity to MCF-7 breast cancer cells at this concentration. Therefore, **38b**, **38l** and **38v** exhibit no cytotoxicity at its effective antibacterial concentration.

<Insert **Fig. 5**>

4. Conclusion

Three series of novel 15-membered 11a-azahomoclarithromycin derivatives (the series **A**-**C**) with the 1, 2, 3-triazole side chains were designed and synthesized through creatively opening the ring of CAM, expanding the ring properly and introducing a suitable side chain of 1, 2, 3-triazole at the C12 and C13 positions, and evaluated for their antibacterial activity against drug-sensitive and -resistant strains. The antibacterial results indicated that the 15-membered 11a-azahomoclarithromycin derivatives exhibited excellent activity against sensitive bacterial strains and greatly improved activity against resistant bacterial strains. Among them, **38b**, **38l** and **38v** displayed the most potent activity against sensitive bacterial strains *S. aureus* ATCC25923 (0.25 μg/mL) and *B. subtilis* ATCC9372 (0.25 μg/mL), while **9e** and **38g** exerted the strongest activity against resistant bacterial strains *S. pneumoniae* AB11 expressing the *erm*B and *mef*A genes (8 μg/mL). In addition, the determination of MBC indicated that the most promising compounds **38b**, **38l**, **38v**, **9e** and **38g** were excellent bacteriostatic agents. Further, the bactericidal curve demonstrated that **A5** exhibited antibacterial activity through bacteriostatic mechanism. Finally, **38b**, **38l** and **38v** were confirmed to be non-toxic to MCF-7 breast cancer cells up to a concentration of 32 μg/mL in preliminary cytotoxicity assay.

Therefore, **38b**, **38l**, **38v**, **9e** and **38g** can be served as lead compounds to provide a new perspective for further structural optimization.

5. Experimental section

5.1. Synthetic procedures

All reagents and solvents were commercially available and could be used directly without purification unless were specifically stated. TLC was used to monitor the reactions process. Column chromatography was used to separate and purify intermediates and compounds. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz, respectively. And $CDCl_3$, d_6-DMSO and C_5D_5N were used as solvents in those spectra. Mass spectra and HRMS were measured by the API 4000 instrument and Orbitrap analyzer, respectively. The melting points of derivatives were performed by an uncorrected RY-1 melting point apparatus.

5.1.1. Synthesis of 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin derivatives (Series A)

5.1.1.1. (R)-1-chloro-3-(4-phenyl-1H-1, 2, 3-triazol-1-yl)propan-2-ol (**13**)

To a solution of R-epichlorohydrin **10** (1 g, 10.9 mmol) in AcOH (10 mL) and H_2O (10 mL) was added NaN_3 (3.7 g, 56.9 mmol) at room temperature. The reaction mixture was warmed to 30 ^{o}C and stirred for 5 h. EtOAc (20 mL) was added, the organic phase was separated and aqueous layer was extracted with EtOAc (20 mL×3). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (PE/ EtOAc = 6:1) to afford azide **11** (1.27 g, 86%) as a light yellow oil.

To a solution of azide **11** (0.5 g, 3.70 mmol) in 75% CH_3OH (20 mL) was added sequentially phenylacetylene **12** (0.38 g, 3.70 mmol), $CuSO_4$ (37 mg), and L-ascorbic acid sodium salt (111 mg). The reaction was stirred at 35~40 ^{o}C for 24 h. The reaction mixture was concentrated and the residue was diluted with DCM (20 mL) and H_2O (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH = 30:1) to give chlorohydrin **13** (0.81 g, 92%) as a white solid. Mp: 102–104 °C, TLC R_f = 0.32 (DCM/CH_3OH = 30:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 (s, 1H), 7.72 – 7.70 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 4.69 (dd, *J* = 13.9, 3.2 Hz, 1H), 4.51 (dd, *J* = 13.9, 7.1 Hz,

1H), 4.45 – 4.41 (m, 1H), 3.63 (d, *J* = 5.5 Hz, 2H); MS (ESI) m/z calcd for $C_{11}H_{12}ClN_3O$ $[M + H]^+$: 238.1, found: 238.3.

5.1.1.2. (S)-1-amino-3-(4-phenyl-1H-1, 2, 3-triazol-1-yl)propan-2-ol (**5a**)

To a solution of chlorohydrin **13** (0.81 g, 3.4 mmol) in CH_3CN (2 mL) was added NaOH solution (10 mL, 10 M). The reaction was stirred at room temperature for 2 h. DCM (20 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were concentrated to afford epoxy **14** as a white solid. The epoxy **14** was used directly for the next step without purification.

To a solution of epoxy **14** in CH_3CN (2 mL) was added 25% aqueous ammonia (20 mL) at room temperature. The reaction was stirred at room temperature for 3 h. DCM (20 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×3). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1) to afford the substituted ethanolamine **5a** (0.42 g, 56% in two steps from **13**) as a white solid. Mp: 131–133 °C, TLC R_f = 0.11 (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1); ^{1}H NMR (600 MHz, DMSO-d_6, δ ppm): 8.49 (s, 1H), 7.86 – 7.85 (m, 2H), 7.46 – 7.43 (m, 2H), 7.34 – 7.31 (m, 1H), 5.13 (s, 1H), 4.52 (dd, *J* = 13.8, 4.0 Hz, 1H), 4.30 (dd, *J* = 13.8, 7.7 Hz, 1H), 3.80 (d, *J* = 5.2 Hz, 1H), 2.58 – 2.52 (m, 2H), 1.59 (s, 2H); MS (ESI) m/z calcd for $C_{11}H_{14}N_4O$ $[M + H]^+$: 219.1, found: 219.4.

5.1.1.3. 9-dihydro-6-O-methylerythromycin A (**2**)

$NaBH_4$ (6 g, 158.6 mmol) was added to a solution of CAM **1** (20 g, 26.8 mmol) in anhydrous THF (150 mL) and CH_3OH (300 mL) in three batches within 1 h at 0 °C. The reaction mixture was stirred at room temperature for 24 h under N_2. The reaction mixture was concentrated, then DCM (200 mL) and saturated NH_4Cl solution (200 mL) were added to the resulting residue. The organic phase was separated and aqueous layer was extracted with DCM (100 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 30:1:0.1~20:1:0.1~10:1:0.1) to afford 9(S)-OH-**2** (10.5 g, 52%) as a white solid. Mp: 208–210 °C, TLC R_f = 0.45 (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 5.73 (d, *J* = 9.8 Hz, 1H), 5.30 (s, 1H), 5.22 (dd, *J* = 11.2, 2.2 Hz, 1H),

4.98 (dd, *J* = 20.3, 4.7 Hz, 1H), 4.51 (d, *J* = 7.1 Hz, 1H), 4.34 (d, *J* = 1.6 Hz, 1H), 4.05 – 4.03 (m, 1H), 3.83 – 3.72 (m, 3H), 3.53 – 3.45 (m, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 3.29 – 3.21 (m, 2H), 3.04 – 2.95 (m, 3H), 2.39 – 2.33 (m, 7H), 2.19 – 2.13 (m, 2H), 2.02 – 1.84 (m, 4H), 1.53 – 1.44 (m, 4H), 1.38 (s, 3H), 1.32 – 1.22 (m, 15H), 1.13 – 1.08 (m, 9H), 0.85 (t, *J* = 7.4 Hz, 3H); MS (ESI) m/z calcd for $C_{38}H_{71}NO_{13}$ $[M + H]^+$: 750.5, found: 750.8.

5.1.1.4. 2', 4", 9(S)-triethylsilane-6-O-methylerythromycin A (**3**)

Imidazole (7.2 g, 105.8 mmol) and **2** (8 g, 10.7 mmol) were dissolved in anhydrous DMF (100 mL) at room temperature. TESCl (5.5 g, 36.5mmol) was added dropwise to the mixture at 0 ^oC. The reaction mixture was stirred at room temperature for 18 h under N_2. EtOAc (100 mL) and n-hexane (100 mL) were added, the organic phase was separated and washed with distilled water (100 mL). The organic layer was dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (PE/acetone = 80:1~50:1~30:1~10:1) to give silane protected product **3** (7.9 g, 68%) as a white foam. Mp: 86–89 °C, TLC R_f = 0.76 (PE/acetone = 3:1); ^1H NMR (600 MHz, $CDCl_3$, δ ppm): 5.09 (dd, *J* = 11.2, 2.3 Hz, 1H), 4.86 (d, *J* = 4.6 Hz, 1H), 4.48 (s, 1H), 4.32 (d, *J* = 7.0 Hz, 1H), 4.26 – 4.24 (m, 1H), 3.89 (d, *J* = 9.7 Hz, 1H), 3.80 (s, 1H), 3.64 (d, *J* = 9.0 Hz, 1H), 3.51 – 3.48 (m, 1H), 3.36 – 3.32 (m, 4H), 3.29 (s, 3H), 3.25 – 3.21 (m, 2H), 3.13 (dd, *J* = 9.7, 7.0 Hz, 1H), 2.88 – 2.86 (m, 1H), 2.54 – 2.50 (m, 1H), 2.39 (d, *J* = 14.8 Hz, 1H), 2.19 (s, 6H), 2.10 –2.09 (m, 1H), 1.97 – 1.95 (m, 1H), 1.85 – 1.82 (m, 1H), 1.69 (d, *J* = 14.3 Hz, 1H), 1.64 – 1.61 (m, 1H), 1.52 (d, *J* = 5.0 Hz, 1H), 1.49 – 1.46 (m, 4H), 1.29 – 0.96 (m, 44H), 0.96 – 0.89 (m, 10H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.71 – 0.54 (m, 18H); MS (ESI) m/z calcd for $C_{56}H_{113}NO_{13}Si_3$ $[M + 2H]^{2+}/2$: 546.9, found: 547.4.

5.1.1.5. Ring-opening intermediate with carboxylic acid (**7a**)

To a solution of silane protected product **3** (375 mg, 0.34 mmol) in $CHCl_3$ (20 mL) was added $Pb(OAc)_4$ (183mg, 0.41 mmol) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 0.5 h under N_2. The aldehyde intermediate **4** was prepared and used directly for the next step without purification.

5a (150 mg, 0.69 mmol) and $NaBH(OAc)_3$ (218 mg, 1.03mmol) were added to the solution of **4** at room temperature. The reaction mixture was stirred at room temperature for 4 h under N_2, then 37% aqueous formaldehyde solution (167 mg, 2.06 mmol) and $NaBH(OAc)_3$ (218 mg, 1.03mmol) were added. The reaction mixture was stirred at room temperature for 4 h. A saturated $NaHCO_3$ (20 mL)

was added,

the organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/NH_3·H_2O = 30:1:0.1) to afford crude product of ester **6a** as a colorless oil.

To a solution of intermediate **6a** in THF-C_2H_5OH-H_2O (20 mL, THF/C_2H_5OH/H_2O = 3:1:1) was added LiOH (41mg, 1.71 mmol) at room temperature. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/NH_3·H_2O = 15:1:0.1~10:1:0.1) to afford carboxylic acid **7a** (185 mg, 44% in four steps from intermediate **3**) as a white solid. Mp: 96–98 °C, TLC R_f = 0.42 (DCM/CH_3OH/NH_3·H_2O = 15:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 8.04 (s, 1H), 7.84 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.32 (m, 1H), 4.80 (d, *J* = 4.7 Hz, 1H), 4.58 (dd, *J* = 14.0, 4.1 Hz, 1H), 4.47 – 4.42 (m, 2H), 4.39 (d, *J* = 3.6 Hz, 1H), 4.28 – 4.25 (m, 1H), 3.93 (dd, *J* = 6.4, 2.4 Hz, 1H), 3.74 – 3.72 (m, 1H), 3.61 (m, 1H), 3.30 (s, 3H), 3.24 – 3.16 (m, 7H), 3.06 (d, *J* = 11.3 Hz, 1H), 2.76 (s, 1H), 2.54 (s, 3H), 2.49 (s, 1H), 2.39 – 2.22 (m, 5H), 2.20 (s, 6H), 1.78 (m, 1H), 1.60 – 1.57 (m, 2H), 1.47 (dd, *J* = 14.9, 4.9 Hz, 1H), 1.28 (s, 3H), 1.26 (m, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.18 – 1.13 (m, 10H), 1.08 – 1.07 (m, 6H), 0.99 – 0.90 (m, 30H), 0.68 – 0.57 (m, 18H); MS (ESI) m/z calcd for $C_{63}H_{119}N_5O_{12}Si_3$ $[M + 2H]^{2+}/2$: 611.9, found: 612.3.

5.1.1.6. 15-membered 11a-azahomoclarithromycin intermediate (**8a**)

To a solution of intermediate **7a** (185 mg, 0.15 mmol) in THF (3 mL) was added sequentially triethylamine (153 mg, 1.51 mmol), 2, 4, 6-trichlorobenzoyl chloride (111 mg, 0.46 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h under N_2. The solution was added to a refluxed solution of DMAP (466 mg, 3.78 mmol) in CH_3CN (30 mL) for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (PE/acetone = 15:1~10:1) to afford cyclic intermediate **8a** (90 mg, 49%) as a white solid. Mp: 96–98 °C, TLC R_f = 0.53 (PE/acetone = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.83 – 7.81 (m, 2H), 7.77 (s, 1H), 7.44 – 7.41 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 5.25 (s, 1H), 4.81 (d, *J* = 4.2 Hz, 1H), 4.73 – 4.70 (m, 1H), 4.58 (dd, *J* = 14.2, 6.6 Hz, 1H), 4.39 (d, *J* = 6.9 Hz, 1H), 4.26 – 4.23 (m, 1H), 4.06 (s, 1H), 3.65 (d, *J* = 8.0 Hz, 1H), 3.54 (m, 1H), 3.34 (s, 1H), 3.27 (s, 3H), 3.20 – 3.13 (m, 5H), 2.76 –

2.70 (m, 2H), 2.59 – 2.44 (m, 3H), 2.34 – 2.26 (m, 4H), 2.19 (s, 6H), 2.13 – 2.10 (m, 1H), 1.98 (m, 1H), 1.93 – 1.92 (m, 1H), 1.83 – 1.81 (m, 1H), 1.63 – 1.57 (m, 2H), 1.43 (dd, *J* = 14.8, 4.6 Hz, 1H), 1.31 (s, 3H), 1.25 – 1.21 (m, 4H), 1.16 – 1.07 (m, 13H), 0.99 – 0.92 (m, 33H), 0.68 – 0.56 (m, 18H); MS (ESI) m/z calcd for $C_{63}H_{117}N_5O_{11}Si_3$ $[M + 2H]^{2+}/2$: 602.9, found: 603.2.

5.1.1.7. 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin (**9a**)

To a solution of cyclic intermediate **8a** (90 mg, 0.07 mmol) in THF (5 mL) was added hydrogen fluoride–pyridine (46 mg, 0.30 mmol, 65%) at room temperature. The reaction mixture was stirred at room temperature for 18 h. A saturated solution of $NaHCO_3$ was added until the pH >7 and the mixture was stirred for 10 min. DCM (20 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1) to afford compound **9a** (31 mg, 48%) as a white solid. Mp: 126–129 °C, TLC R_f = 0.40 (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 – 7.82 (m, 2H), 7.78 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 4.86 (d, *J* = 4.7 Hz, 1H), 4.59 (dd, *J* = 14.5, 4.6 Hz, 1H), 4.51 (dd, *J* = 14.5, 5.4 Hz, 1H), 4.39 (d, *J* = 7.2 Hz, 1H), 4.32 (s, 1H), 4.06 – 4.03 (m, 1H), 3.72 (d, *J* = 8.1 Hz, 1H), 3.49 (dd, *J* = 14.6, 5.5 Hz, 2H), 3.27 (s, 3H), 3.23 – 3.21 (m, 5H), 2.99 – 2.93 (m, 2H), 2.71 (dd, *J* = 13.3, 11.4 Hz, 1H), 2.57 – 2.36 (m, 5H), 2.36 – 2.30 (m, 9H), 2.26 – 2.23 (m, 2H), 2.18 – 2.14 (m, 1H), 1.88 – 1.86 (m, 1H), 1.75 – 1.72 (m, 2H), 1.44 (dd, *J* = 15.2, 4.9 Hz, 1H), 1.32 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.23 – 1.18 (m, 10H), 1.08 (d, *J* = 7.3 Hz, 3H), 0.85 (d, *J* = 7.1 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.26, 148.00, 130.38, 128.90, 128.90, 128.30, 125.72, 125.72, 120.39, 103.52, 96.20, 80.22, 79.10, 78.94, 78.10, 72.62, 71.07, 68.85, 67.91, 65.42, 65.27, 62.96, 59.09, 51.74, 50.13, 49.44, 45.37, 44.24, 41.41, 40.41, 36.65, 34.94, 32.54, 30.95, 29.71, 29.26, 22.17, 21.55, 21.39, 18.26, 14.66, 10.63; HRMS (ESI) m/z calcd for $C_{45}H_{75}N_5O_{11}$ $[M + H]^+$: 862.5463, found: 862.5723.

According to the synthetic procedure described above, the following compounds (**9b**-**9l**) were also prepared:

5.1.1.8. Compound (**9b**)

White solid, yield 59%, mp: 126–129 °C, TLC R_f = 0.40 (DCM/CH_3OH/$NH_3 \cdot H_2O$ = 10:1:0.1); ^1H NMR (600 MHz, $CDCl_3$, δ ppm): 7.83 – 7.73 (m, 3H), 7.52 – 7.40 (m, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 5.16 (s, 1H), 4.80 (s, 1H), 4.72 – 4.60 (m, 2H), 4.46 – 4.41 (m, 1H), 4.05 – 4.02 (m, 1H), 3.90 (s, 1H), 3.81 (s, 1H), 3.63 – 3.40 (m, 2H), 3.26 (s, 3H), 3.22 – 2.91 (m, 6H), 2.77 – 2.48 (m, 5H), 2.42 – 1.83 (m, 12H), 1.81 –1.61 (m, 4H), 1.59 – 1.09 (m, 20H), 1.09 (d, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 172.53, 146.83, 129.49, 127.82, 127.82, 127.18, 124.73, 124.73, 119.35, 102.36, 95.53, 79.33, 79.06, 78.42, 77.03, 76.88, 71.56, 70.86, 70.06, 67.73, 64.85, 64.69, 64.40, 50.40, 49.17, 48.42, 48.39, 44.38, 39.40, 37.21, 35.98, 34.11, 31.80, 29.41, 28.68, 28.31, 20.60, 20.51, 20.43, 20.35, 20.27, 17.57, 9.96, 9.11; HRMS (ESI) m/z calcd for $C_{45}H_{75}N_5O_{11}$ $[M + H]^+$: 862.5463, found: 862.5709.

Physical characteristics, ^1H NMR, ^{13}C NMR, MS and HRMS for other target compounds of series A, were reported in the supporting information.

5.1.2. Synthesis of 15-membered 11a-aza-12-(1, 2, 3-triazoles)homoclarithromycin derivatives (Series B)

5.1.2.1. (S)-methyl 2-[(tert-butoxycarbonyl)amino]-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate (**26**)

To a solution of N-Boc-L-serine methyl ester **24** (2 g, 9.1 mmol) in anhydrous DCM (50 mL) was added Et_3N (2 g, 19.8 mmol) at room temperature. A solution of MsCl (1.15 g, 10 mmol) in anhydrous DCM (10 mL) was added dropwise to the mixture at 0 ^oC under N_2. The reaction mixture was stirred at 0 ^oC for 0.5 h under N_2. H_2O (50 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (30 mL×2). The combined layers were concentrated to form methanesulfonate **25** as a colorless oil. The crude intermediate **25** was used directly for the next step without purification.

To a solution of methanesulfonate **25** in DMF (60 mL) was added NaN_3 (1.4 g, 21.5 mmol) at room temperature. The reaction mixture was stirred at 50 ^oC for 0.5 h. EtOAc (60 mL) and H_2O (60 mL) were added, the organic phase was separated and aqueous layer was extracted with EtOAc (60 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was concentrated *in vacuo* to afford the azide **26** (8.74g) as a colorless oil.

To a solution of azide **26** (4.37 g) in 75% CH_3OH (20 mL) was added sequentially phenylacetylene **12** (0.21 g, 2.06 mmol), $CuSO_4$ (41 mg), and L-ascorbic acid sodium salt (123 mg) at

room temperature. The reaction mixture was stirred at 35~40 °C for 48 h. The reaction mixture was concentrated and the residue was diluted with DCM (20 mL) and H_2O (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (PE/EtOAc = 4:1~1:1) to afford 1, 2, 3-triazole intermediate **27** (0.37 g, 23% in three steps from **24**) as a white solid. Mp: 118–120 °C, TLC R_f = 0.58 (DCM/MeOH = 30:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.82 – 7.81 (m, 2H), 7.73 (s, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 5.42 (d, J = 6.6 Hz, 1H), 4.92 (dd, *J* = 14.0, 3.8 Hz, 1H), 4.86 (dd, *J* = 14.0, 4.4 Hz, 1H), 4.76 (d, *J* = 3.3 Hz, 1H), 3.81 (s, 3H), 1.45 (s, 9H); MS (ESI) m/z calcd for $C_{17}H_{22}N_4O_4$ $[M + H]^+$: 347.2, found: 347.4.

5.1.2.2. (S)-2-amino-3-(4-phenyl-1H-1, 2, 3-triazol-1-yl)propan-1-ol (**19a**)

To a solution of 1, 2, 3-triazol intermediate **27** (0.37 g, 1.07 mmol) in CH_3OH (20 mL) was added $NaBH_4$ (121 mg, 3.20 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated and the residue was diluted with DCM (20 mL) and H_2O (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were concentrated to afford alcohol **28** as a white solid.

To a solution of alcohol **28** in EtOAc (10 mL) was added concentrated HCl (4 mL, 48 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h. A saturated solution of $NaHCO_3$ was added until the pH >7 and the mixture was stirred for 10 min. The resulting mixture was concentrated *in vacuo* and the residue was purified by silica gel column ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 10:1:0.1) to afford substituted ethanolamine **19a** (0.14 g, 60% in two steps from **27**) as a white solid. Mp: 121–123 °C, TLC R_f = 0.36 ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 10:1:0.1); ^{1}H NMR (600 MHz, DMSO-d_6, δ ppm): 8.53 (s, 1H), 7.85 – 7.83 (m, 2H), 7.46 – 7.43 (m, 2H), 7.34 – 7.31 (m, 1H), 4.48 (dd, J = 13.6, 4.9 Hz, 1H), 4.23 (dd, J = 13.6, 7.8 Hz, 1H), 3.35 – 3.31 (m, 2H), 3.14 – 3.11 (m, 1H), 1.91 (s, 1H); MS (ESI) m/z calcd for $C_{11}H_{14}N_4O$ $[M + H]^+$: 219.1, found: 219.4.

5.1.2.3. Ring-opening intermediate with carboxylic acid (**21a**)

To a solution of silane protected product **3** (350 mg, 0.32 mmol) in $CHCl_3$ (20 mL) was added $Pb(OAc)_4$ (171mg, 0.39 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h under N_2.

The aldehyde intermediate **4** was prepared and used directly for the next step without purification.

19a (140 mg, 0.64 mmol) and $NaBH(OAc)_3$ (204 mg, 0.96 mmol) were added to the solution of **4** at room temperature. The reaction mixture was stirred at room temperature for 4 h under N_2, then 37% aqueous formaldehyde solution (156 mg, 1.92 mmol) and $NaBH(OAc)_3$ (204 mg, 0.96 mmol) were added. The reaction mixture was stirred at room temperature for 4 h. The saturated $NaHCO_3$ (20 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 30:1:0.1) to afford crude product of ester **20a** as a colorless oil.

To a solution of intermediate **20a** in THF-C_2H_5OH-H_2O (20 mL, $THF/C_2H_5OH/H_2O$ = 3:1:1) was added LiOH (38mg, 1.59 mmol) at room temperature. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 15:1:0.1~10:1:0.1) to afford carboxylic acid **21a** (200 mg, 51% in four steps from **3**) as a white solid. Mp: 78–81 °C, TLC R_f = 0.42 ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 15:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.83 – 7.81 (m, 2H), 7.77 (s, 1H), 7.44 – 7.41 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 5.25 (s, 1H), 4.81 (d, *J* = 4.2 Hz, 1H), 4.73 – 4.70 (m, 1H), 4.58 (dd, *J* = 14.2, 6.6 Hz, 1H), 4.39 (d, *J* = 6.9 Hz, 1H), 4.26 – 4.23 (m, 1H), 4.06 (s, 1H), 3.65 (d, *J* = 8.0 Hz, 1H), 3.54 (s, 1H), 3.34 (s, 1H), 3.27 (s, 3H), 3.20 – 3.13 (m, 5H), 2.76 – 2.70 (m, 2H), 2.59 – 2.44 (m, 3H), 2.34 – 2.26 (m, 4H), 2.19 (s, 6H), 2.13 – 2.10 (m, 1H), 1.98 (m, 1H), 1.92 (m, 1H), 1.83 – 1.81 (m, 1H), 1.62 – 1.57 (m, 2H), 1.43 (dd, *J* = 14.8, 4.6 Hz, 1H), 1.31 (s, 3H), 1.25 – 1.21 (m, 4H), 1.16 – 1.07 (m, 13H), 0.99 – 0.92 (m, 33H), 0.68 – 0.56 (m, 18H); MS (ESI) m/z calcd for $C_{63}H_{119}N_5O_{12}Si_3$ $[M + 2H]^{2+}/2$: 611.9, found: 611.8.

5.1.2.4. 15-membered 11a-azahomoclarithromycin intermediate (**22a**)

To a solution of intermediate **21a** (200 mg, 0.16 mmol) in THF (3 mL) was added sequentially triethylamine (166 mg, 1.64 mmol), 2, 4, 6-trichlorobenzoyl chloride (120 mg, 0.49 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h under N_2. The solution was added to a refluxed solution of DMAP (504 mg, 4.09 mmol) in CH_3CN (30 mL) for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (PE/acetone = 15:1~10:1) to afford cyclic intermediate **22a** (70 mg, 36%) as a white solid. Mp: 60–

63 °C, TLC R_f = 0.53 (PE/acetone = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 – 7.78 (m, 3H), 7.44 – 7.40 (m, 2H), 7.35 – 7.32 (m, 1H), 4.70 (s, 1H), 4.47 – 4.40 (m, 2H), 4.27 – 4.26 (m, 1H), 4.17 – 3.97 (m, 3H), 3.74 – 3.71 (m, 1H), 3.59 – 3.58 (m, 1H), 3.50 – 3.49 (m, 1H), 3.29 – 3.25 (m, 3H), 3.22 – 3.14 (m, 5H), 2.63 (s, 2H), 2.45 – 2.28 (m, 7H), 2.20 (s, 6H), 2.13 (m, 1H), 2.02 (m, 1H), 1.77 – 1.76 (m, 2H), 1.52 – 1.48 (m, 2H), 1.43 – 1.39 (m, 1H), 1.26 (s, 3H), 1.25 – 1.24 (m, 1H), 1.20 (d, *J* = 5.5 Hz, 3H), 1.16 – 1.11 (m, 10H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.00 – 0.92 (m, 33H), 0.67 – 0.55 (m, 18H); MS (ESI) m/z calcd for $C_{63}H_{117}N_5O_{11}Si_3$ $[M + 2H]^{2+}/2$: 602.9, found: 603.3.

5.1.2.5. 15-membered 11a-aza-12-(1, 2, 3-triazoles)homoclarithromycin (**23a**)

To a solution of cyclic intermediate **22a** (70 mg, 0.06 mmol) in THF (5 mL) was added hydrogen fluoride–pyridine (26 mg, 0.17 mmol, 65%) at room temperature. The reaction mixture was stirred at room temperature for 18 h. A saturated solution of $NaHCO_3$ was added until the pH >7 and the mixture was stirred for 10 min. DCM (20 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1) to afford compound **23a** (30 mg, 60%) as a white solid. Mp: 108–110 °C, TLC R_f = 0.40 (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.88 (s, 1H), 7.83 (dd, *J* = 10.2, 3.1 Hz, 2H), 7.44 (dd, *J* = 10.0, 5.4 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 4.78 (d, *J* = 4.4 Hz, 1H), 4.48 – 4.39 (m, 3H), 4.22 (d, *J* = 10.1 Hz, 1H), 4.10 – 3.95 (m, 3H), 3.79 (d, *J* = 5.9 Hz, 1H), 3.50 – 3.46 (m, 2H), 3.29 – 3.14 (m, 7H), 3.01 (t, *J* = 9.5 Hz, 1H), 2.95 – 2.84 (m, 2H), 2.55 – 2.21 (m, 14H), 2.15 – 1.96 (m, 3H), 1.86 – 1.83 (m, 1H), 1.81 – 1.75 (m, 1H), 1.71 – 1.63 (m, 1H), 1.52 (s, 1H), 1.31 (s, 3H), 1.30 – 1.21 (m, 10H), 1.18 (d, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 175.50, 147.94, 130.55, 128.86, 128.86, 128.17, 125.71, 125.71, 120.37, 103.12, 95.54, 80.72, 79.65, 78.82, 78.40, 78.00, 72.77, 70.90, 68.94, 67.99, 65.55, 65.50, 62.96, 62.01, 50.33, 49.45, 47.92, 44.11, 40.36, 39.73, 36.68, 35.06, 34.82, 34.50, 29.71, 28.86, 25.62, 21.62, 21.37, 20.85, 18.17, 13.38, 10.93; HRMS (ESI) m/z calcd for $C_{45}H_{75}N_5O_{11}$ $[M + H]^+$: 862.5463, found: 862.5537.

According to the synthetic procedure described above, the following compounds (**23b**-**23l**) were also prepared:

5.1.2.6. Compound (**23b**)

White solid, yield 80%, mp: 120–122 °C, TLC R_f = 0.40 (DCM/CH_3OH/NH_3·H_2O = 10:1:0.1); ^1H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 (d, *J* = 9.3 Hz, 3H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 4.90 (d, *J* = 4.5 Hz, 1H), 4.52 – 4.42 (m, 3H), 4.35 (dd, *J* = 13.9, 6.3 Hz, 1H), 4.10 – 4.00 (m, 2H), 3.89 (dd, *J* = 11.9, 4.0 Hz, 1H), 3.77 (d, *J* = 7.1 Hz, 1H), 3.56 – 3.45 (m, 3H), 3.32 (s, 3H), 3.27 – 3.17 (m, 4H), 3.05 (t, *J* = 9.7 Hz, 1H), 2.94 – 2.87 (m, 1H), 2.68 (dd, *J* = 12.2, 5.8 Hz, 1H), 2.48 (s, 3H), 2.45 – 2.18 (m, 5H), 2.32 (s, 6H), 2.08 – 1.83 (m, 3H), 1.79 – 1.74 (m, 1H), 1.59 (dd, *J* = 15.2, 4.9 Hz, 2H), 1.36 (s, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.24 – 1.21 (m, 7H), 1.19 (d, *J* = 7.3 Hz, 3H), 1.10 (d, *J* = 7.4 Hz, 3H), 0.92 (dd, *J* = 15.4, 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.09, 147.77, 130.52, 128.86, 128.86, 128.19, 125.72, 125.72, 120.45, 102.90, 95.89, 80.48, 79.49, 79.00, 78.17, 78.00, 72.77, 71.05, 68.75, 65.68, 65.42, 62.58, 62.02, 50.60, 49.45, 44.67, 41.25, 40.38, 36.24, 35.02, 31.52, 29.05, 21.59, 21.43, 21.00, 18.36, 14.35, 10.17; HRMS (ESI) m/z calcd for $C_{45}H_{75}N_5O_{11}$ $[M + H]^+$: 862.5463, found: 862.5610.

Physical characteristics, ^1H NMR, ^{13}C NMR, MS and HRMS for other target compounds of series B, were reported in the supporting information.

5.1.3. Synthesis of 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin derivatives (Series C)

5.1.3.1. 4-(bromomethyl)-1-phenyl-1H-1, 2, 3-triazole (**44**)

To a solution of aniline **39** (2 g, 21.49 mmol) in H_2O (30 mL) was added sequentially concentrated HCl (9 mL, 108 mmol), $NaNO_2$ (1.78g, 25.80 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. A solution of NaN_3 (2.37 g, 36.46 mmol) in H_2O (10 mL) was added dropwise to the mixture at 0 °C. This reaction mixture was stirred at 0 °C for 0.5 h and stirred at room temperature for 4 h. Then DCM (50 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (30 mL×2). The combined organic layers were concentrated to afford azide intermediate **40** (2.48g, 97%) as a reddish brown oil.

To a solution of azide **40** (2.48 g, 20.83 mmol) in 75% CH_3OH (20 mL) was added sequentially methyl propiolate **41** (1.76 g, 20.95 mmol), $CuSO_4$ (235 mg), and L-ascorbic acid sodium salt (705 mg). The reaction mixture was stirred at 35~40 °C for 48 h. The mixture was concentrated and the residue was diluted with DCM (20 mL) and H_2O (20 mL). The organic phase was separated and

aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH = 30:1) to afford methyl ester intermediate **42** (2.09 g, 49%) as a light yellow solid.

The methyl ester intermediate **42** (2.09 g, 10.29 mmol) was added slowly to a suspension of $LiAlH_4$ (1.18 g, 31.09 mmol) in tetrahydrofuran (20 mL) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 1 h. The reaction was quenched by adding H_2O (1.5g) and CH_3OH (20 mL) slowly, then filtered, concentrated to afford the residue. DCM (20 mL) and H_2O (20 mL) were added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was concentrated to afford primary alcohol intermediate **43** (1.7 g, 94%) as a light yellow solid.

To a solution of primary alcohol intermediate **43** (1.7 g, 9.71 mmol) in anhydrous DCM (20 mL) was added PBr_3 (7.89 g, 29.13 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched by adding H_2O (20 mL) slowly, adjusted the pH to 7-8 with $NaHCO_3$. The organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (PE/EtOAc = 4:1) to afford bromine intermediate **44** (1.11 g, 48%) as a white solid. Mp: 126–130 °C, TLC R_f = 0.70 (PE/EtOAc = 2:1); ^1H NMR (600 MHz, $CDCl_3$, δ ppm): 8.02 (s, 1H), 7.74 – 7.72 (m, 2H), 7.56 – 7.53 (m, 2H), 7.48 – 7.45 (m, 1H), 4.66 (s, 2H); MS (ESI) m/z calcd for $C_9H_8BrN_3$ $[M+2+H]^+$: 240.0, found: 240.2.

5.1.3.2. (S)-1-amino-3-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)propan-2-ol (**34a**)

To a solution of (R)-glycidol **45** (187 mg, 2.53 mmol) in anhydrous THF (10 mL) was added 80% NaH (316 mg, 10.53 mmol) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 0.5 h, then a solution of bromine intermediate **44** (500 mg, 2.11 mmol) in anhydrous THF (10 mL) was added dropwise at 0 ^oC under N_2. The reaction was stirred at room temperature overnight under N_2. H_2O (20 mL) and DCM (20 mL) were added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×2). The combined organic layers were concentrated *in vacuo* and the residue was purified by silica gel column (PE/EtOAc = 2:1 ~1:1) to afford epoxy **46** (340 mg, 70%) as a white solid.

To a solution of epoxy **46** (340 mg, 1.47 mmol) in CH_3CN (2 mL) was added 25% aqueous

ammonia (15 mL) at room temperature. The reaction was stirred at room temperature for 3 h. DCM (20 mL) was added, the organic phase was separated and aqueous layer was extracted with DCM (20 mL×3). The combined organic layers were concentrated *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/NH_3·H_2O = 10:1:0.1) to afford substituted ethanolamine **34a** (260 mg, 71%) as a white solid. Mp: 107–109 °C, TLC R_f = 0.11 (DCM/CH_3OH/NH_3·H_2O = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 8.01 (s, 1H), 7.74 – 7.73 (m, 2H), 7.54 – 7.52 (m, 2H), 7.46 – 7.44 (t, *J* = 7.5 Hz, 1H), 4.77 (s, 2H), 3.81 (s, 1H), 3.66 – 3.64 (dd, *J* = 9.6, 3.1 Hz, 1H), 3.59 – 3.56 (m, 1H), 2.81 (d, *J* = 63.1 Hz, 2H); MS (ESI) m/z calcd for $C_{12}H_{16}N_4O_2$ $[M + H]^+$: 249.1, found: 249.3.

5.1.3.3. Ring-opening intermediate with carboxylic acid (**36a**)

To a solution of silane protected product **3** (352 mg, 0.32 mmol) in $CHCl_3$ (20 mL) was added $Pb(OAc)_4$ (171mg, 0.39 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h under N_2. The aldehyde intermediate **4** was prepared and used directly for the next step without purification.

34a (160 mg, 0.64 mmol) and $NaBH(OAc)_3$ (205 mg, 0.97 mmol) were added to the solution of **4** at room temperature. The reaction mixture was stirred at room temperature for 4 h under N_2, then 37% aqueous formaldehyde solution (157 mg, 1.93 mmol) and $NaBH(OAc)_3$ (205 mg, 0.97 mmol) were added. The reaction mixture was stirred at room temperature for 4 h. The saturated $NaHCO_3$ (20 mL) was added and the aqueous phase was extracted with DCM (20 mL×2). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/NH_3·H_2O = 30:1:0.1) to afford crude product of ester **35a** as a colorless oil.

To a solution of ester intermediate **35a** in THF-C_2H_5OH-H_2O (20 mL, THF/C_2H_5OH/H_2O = 3:1:1) was added LiOH (39mg, 1.63 mmol) at room temperature. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM/CH_3OH/NH_3·H_2O = 15:1:0.1~10:1:0.1) to afford carboxylic acid **36a** (250 mg, 62% in four steps from intermediate **3**) as a white solid. Mp: 63–66 °C, TLC R_f = 0.53 (DCM/CH_3OH/NH_3·H_2O = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 8.06 (s, 1H), 7.76 – 7.75 (m, 2H), 7.54 – 7.51 (m, 2H), 7.46 – 7.43 (m, 1H), 4.82 (d, *J* = 4.7 Hz, 1H), 4.76 (s, 2H), 4.46 (d, *J* = 7.0 Hz, 1H), 4.28 – 4.25 (m, 1H), 4.22 – 4.21 (m, 1H), 3.95 – 3.94 (m, 1H), 3.74 – 3.72 (m, 1H), 3.67 (dd, *J* = 9.9, 5.1 Hz, 1H), 3.61 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.57 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.31 (s, 3H), 3.26 (d, *J* = 7.1 Hz, 4H), 3.22 (dd, *J* = 13.5, 7.6 Hz, 2H), 3.09 (d, *J* = 10.9 Hz, 1H), 3.01 – 2.97 (m,

1H), 2.78 (d, *J* = 12.6 Hz, 1H), 2.67 – 2.64 (m, 1H), 2.60 (s, 3H), 2.50 – 2.46 (m, 3H), 2.36 (d, *J* = 14.8 Hz, 2H), 2.20 (s, 6H), 1.81 (dd, *J* = 13.1, 6.8 Hz, 1H), 1.60 – 1.57 (m, 2H), 1.47 (dd, *J* = 14.9, 4.9 Hz, 1H), 1.30 (s, 3H), 1.28 – 1.27 (m, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.17 – 1.15 (m, 10H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 7.4 Hz, 3H), 0.97 – 0.92 (m, 30H), 0.67 – 0.57 (m, 18H); MS (ESI) m/z calcd for $C_{64}H_{121}N_5O_{13}Si_3$ $[M + 2H]^{2+}/2$: 626.9, found: 627.3.

5.1.3.4. 15-membered 11a-azahomoclarithromycin intermediate (**37a**)

To a solution of intermediate **36a** (230 mg, 0.18 mmol) in THF (4 mL) was added sequentially triethylamine (185 mg, 1.83 mmol), 2, 4, 6-trichlorobenzoyl chloride (135 mg, 0.55 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h under N_2. The solution was added to a refluxed solution of DMAP (561 mg, 4.55 mmol) in CH_3CN (40 mL) for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (PE/acetone = 15:1~10:1) to afford cyclic intermediate **37a** (140 mg, 62%) as a white solid. Mp: 62–64 °C, TLC R_f = 0.44 (PE/acetone = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.96 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.54 – 7.52 (m, 2H), 7.46 (dd, *J* = 10.8, 4.1 Hz, 1H), 5.09 (d, *J* = 4.6 Hz, 1H), 4.85 (d, *J* = 4.6 Hz, 1H), 4.75 (dd, *J* = 19.2, 11.6 Hz, 2H), 4.41 (d, *J* = 6.8 Hz, 1H), 4.29 – 4.26 (m, 1H), 4.13 (s, 1H), 3.72 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.66 (d, *J* = 6.3 Hz, 2H), 3.56 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.40 (s, 1H), 3.30 (s, 3H), 3.22 – 3.20 (m, 5H), 2.80 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.72 (s, 1H), 2.47 (d, *J* = 5.6 Hz, 3H), 2.35 – 2.32 (m, 1H), 2.25 (s, 3H), 2.20 (s, 6H), 2.11 (dd, *J* = 11.8, 8.3 Hz, 1H), 1.99 (m, 1H), 1.92 – 1.88 (m, 1H), 1.85 – 1.83 (m, 1H), 1.63 – 1.59 (m, 2H), 1.47 (dd, *J* = 14.9, 4.9 Hz, 1H), 1.30 (s, 3H), 1.25 (s, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.17 – 1.15 (m, 10H), 1.11 (d, *J* = 7.3 Hz, 3H), 0.98 – 0.92 (m, 33H), 0.68 – 0.59 (m, 18H); MS (ESI) m/z calcd for $C_{64}H_{119}N_5O_{12}Si_3$ $[M + 2H]^{2+}/2$: 617.9, found: 618.4.

5.1.3.5. 15-membered 11a-aza-13-(1, 2, 3-triazoles)homoclarithromycin (**38a**)

To a solution of cyclic intermediate **37a** (120 mg, 0.10 mmol) in THF (5 mL) was added hydrogen fluoride–pyridine (44 mg, 0.29 mmol, 65%) at room temperature. The reaction mixture was stirred at room temperature for 18 h. Then the pH of mixture was adjusted to 7-8 with saturated $NaHCO_3$ (20 mL), and the aqueous phase was extracted with DCM (20 mL×3). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel

column (DCM/CH_3OH/NH_3·H_2O = 10:1:0.1) to afford compound **38a** (50 mg, 58%) as a white solid. Mp: 99–101 °C, TLC R_f = 0.26 (DCM/CH_3OH/NH_3·H_2O = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.99 (s, 1H), 7.75 – 7.74 (m, 2H), 7.55 – 7.52 (m, 2H), 7.47 – 7.44 (m, 1H), 5.36 – 5.34 (m, 1H), 4.88 (d, *J* = 4.7 Hz, 1H), 4.75 – 4.69 (m, 2H), 4.41 (d, *J* = 7.2 Hz, 1H), 4.33 (d, *J* = 5.3 Hz, 1H), 4.08 – 4.03 (m, 1H), 3.72 (d, *J* = 7.6 Hz, 1H), 3.64 – 3.57 (m, 3H), 3.50 – 3.47 (m, 1H), 3.29 – 3.24 (m, 8H), 3.00 (d, *J* = 8.7 Hz, 1H), 2.94 – 2.90 (m, 1H), 2.86 (t, *J* = 12.4 Hz, 1H), 2.39 (d, *J* = 6.6 Hz, 5H), 2.34 – 2.18 (m, 11H), 2.06 – 1.94 (m, 2H), 1.78 – 1.70 (m, 2H), 1.46 (dd, *J* = 15.3, 5.0 Hz, 1H), 1.32 (s, 3H), 1.30 (d, *J* = 6.3 Hz, 3H), 1.26 – 1.21 (m, 7H), 1.16 (d, *J* = 7.6 Hz, 3H), 1.06 (d, *J* = 7.3 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.48, 145.57, 137.03, 129.82, 129.82, 128.82, 120.82, 120.54, 120.54, 103.34, 96.04, 80.01, 79.54, 78.38, 78.13, 72.70, 71.26, 70.80, 68.65, 68.06, 65.42, 65.09, 64.73, 62.89, 58.45, 50.06, 49.47, 45.33, 44.25, 42.00, 41.59, 40.46, 37.11, 34.95, 32.72, 30.53, 29.97, 27.03, 22.72, 21.60, 21.37, 18.35, 15.24, 10.38; HRMS (ESI) m/z calcd for $C_{46}H_{77}N_5O_{12}$ $[M + H]^+$: 892.5569, found: 892.5642.

According to the synthetic procedure described above, the following compounds (**38b**-**38v**) were also prepared:

5.1.3.6. Compound (**38b**)

White solid, yield 63%, mp: 174–176 °C, TLC R_f = 0.26 (DCM/CH_3OH/NH_3·H_2O = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 8.01 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.9 Hz, 2H), 7.47 – 7.44 (m, 1H), 5.01 (s, 1H), 4.89 (s, 1H), 4.74 – 4.67 (m, 2H), 4.44 (d, *J* = 7.2 Hz, 2H), 4.10 – 4.06 (m, 1H), 3.88 (s, 1H), 3.77 – 3.58 (m, 3H), 3.52 – 3.42 (m, 2H), 3.39 – 3.12 (m, 8H), 3.04 – 2.96 (m, 2H), 2.89 (s, 1H), 2.71 – 2.21 (m, 14H), 2.18 – 2.10 (m, 2H), 2.00 – 1.91 (m, 2H), 1.84 – 1.80 (m, 1H), 1.67 – 1.65 (m, 1H), 1.50 (d, *J* = 10.8 Hz, 1H), 1.35 – 1.22 (m, 13H), 1.17 (d, *J* = 7.8 Hz, 3H), 1.09 (d, *J* = 5.5 Hz, 3H), 0.97 – 0.83 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.48, 145.57, 137.03, 129.82, 129.82, 128.82, 120.82, 120.54, 120.54, 103.34, 96.04, 80.01, 79.54, 78.38, 78.13, 72.70, 71.26, 70.80, 68.65, 68.06, 65.42, 65.09, 64.73, 62.89, 58.45, 50.06, 49.47, 45.33, 44.25, 42.00, 41.59, 40.46, 37.11, 34.95, 32.72, 30.53, 29.97, 27.03, 22.72, 21.60, 21.37, 18.35, 15.24, 10.38. HRMS (ESI) m/z calcd for $C_{46}H_{77}N_5O_{12}$ $[M + H]^+$: 892.5569, found: 892.5632.

Physical characteristics, ^{1}H NMR, ^{13}C NMR, MS and HRMS for other target compounds of series C, were reported in the supporting information.

5.2. In vitro antibacterial assay

According to the broth microdilution method of the Clinical and Laboratory Standards Institute rules, the minimum inhibitory concentration (MIC) values of the prepared compounds and the two control drugs (CAM and AZM) were determined in 96-well plates. A series of gradient solutions of the prepared compounds and the two control drugs were prepared in cation adjusted Mueller-Hinton (CAMH) by using a 2-fold dilution method with concentrations ranging from 0.25 to 128 μg/mL or from 0.5 to 256 μg/mL. After log-phase bacteria were added to the above solutions, 96-well plates were placed in a thermostat and incubated for 24 h at 37 ^{o}C. By observing the turbidity, the solution of the last well was clear, and the corresponding concentration of the well was the MIC value.

5.3. Minimum bactericidal concentration (MBC) assay

The determination of MBC value was based on the above described determination of MIC value. After 24 h of incubation, by observing the turbidity, if the solution in the well was clear, the solution was plated onto tryptic soy agar (TSA) plates. The TSA plates were placed in a thermostat and incubated for 24 h at 37 ^{o}C. We observed whether there were colonies on TSA plates. If there were no colonies, the corresponding minimum concentration was the MBC value.

5.4. Time-kill curve assay

A series of concentrations (0.5, 1, 2 and 4 MIC, MIC=8 μg/mL) of compound **9e** were prepared in CAMH broth. The above solutions also contained log-phase *S. pneumoniae* AB11 at a concentration of approximate 10^{6} CFU/mL. Cultures were incubated at 37 ^{o}C with shaking. The 20 μL samples were removed from cultures at 0, 3, 6, 9, 12 and 24 h, respectively. 20 μL samples were diluted 10-fold with 180 μL CAMH broth and mixed evenly. The resulting diluted samples were further diluted 10-fold as the above described method. Finally, we obtained 10 samples with concentration gradient. And 5 μL volumes from 10 samples were plated onto TSA plates, which all TSA plates were incubated for 24 h at 37 ^{o}C. After that, the CFU/mL values were obtained by counting the number of colonies at each time point.

5.5. MTT cytotoxicity assay

The toxicity of compounds **38b**, **38l** and **38v** to MCF-7 breast cancer cells was determined by 28 h continuous MTT assay. After the cells (10^4 cell/well) were incubated in a 96-well plate overnight, then 100 μl of each compound were added. After incubation for 24 h, the MTT solution (5 mg/mL) was added and incubation was continued for 4 h at 37 °C. The MTT solution was removed and then DMSO was added. After adding DMSO for 10 min, then their absorbance was determined at 570 nm.

Conflicts 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 to this article can be found online at https://

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Figure captions

Fig. 1. Chemical structures of some macrolide antibiotics

Fig. 2. Feasible synthetic strategy of an 11a-azalide skeleton

Fig. 3. Corresponding configurations of some representative intermediates

Fig. 4. Time-kill curves of compound **9e** against *S. pneumoniae* AB11

Fig. 5. Cytotoxicity profile of compound **38b**, **38l** and **38v** against MCF-7 breast cancer cells. CAM was used as a control and DMSO as the vehicle control in cytotoxicity assay.

Scheme 1. Regents and conditions: (a) $NaBH_4$, CH_3OH-THF, rt, 24 h, 52%; (b) TESCl, imidazole, DMF, 0 ^oC to rt, 18 h, 68%; (c) $Pb(OAc)_4$, $CHCl_3$, 0 ^oC, 0.5 h; (d) **5a-l**, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (e) HCHO, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (f) LiOH, THF-C_2H_5OH-H_2O, rt, 6 h, 38~75% in four steps from intermediate **3**; (g) i) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, THF, rt, 4 h; ii) DMAP, CH_3CN, reflux, 0.5 h, 42~69%; (h) Hydrogen fluoride-pyridine (65% in hydrofluoric acid), THF, rt, 18 h, 32~68%.

Scheme 2. Regents and conditions: (a) NaN_3, AcOH-H_2O, 30 ^oC, 5 h, 86~90%; (b) **12**, $CuSO_4$, L-ascorbic acid sodium salt, CH_3OH-H_2O, 35~40 ^oC, 24 h, 64~93%; (c) NaOH, CH_3CN-H_2O, rt, 2 h; (d) 25% $NH_3 \cdot H_2O$, CH_3CN, rt, 3 h, 16~67% in two steps.

Scheme 3. Regents and conditions: (a) **19a-l**, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (b) HCHO, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (c) LiOH, THF-C_2H_5OH-H_2O, rt, 6 h, 18~88% in four steps from **3**; (d) i) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, THF, rt, 4 h; ii) DMAP, CH_3CN, reflux, 0.5 h, 22~76%; (e) Hydrogen fluoride-pyridine (65% in hydrofluoric acid), THF, rt, 18 h, 26~93%.

Scheme 4. Regents and conditions: (a) MsCl, DCM, Et_3N, 0 ^oC, 0.5 h; (b) NaN_3, DMF, 50 ^oC, 0.5 h; (c) **12**, $CuSO_4$, L-ascorbic acid sodium salt, CH_3OH-H_2O, 35~40 ^oC, 48 h, 17~40% in three steps; (d) $NaBH_4$, CH_3OH, 0 ^oC, 2 h; (e) aq HCl, EtOAc, rt, 4 h, 20~78% in two steps.

Scheme 5. Regents and conditions: (a) **34a-v**, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (b) HCHO, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (c) LiOH, THF-C_2H_5OH-H_2O, rt, 6 h, 37~86% in four steps from intermediate **3**; (d) i) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, THF, rt, 4 h; ii) DMAP, CH_3CN, reflux, 0.5 h, 27~88%; (e) Hydrogen fluoride-pyridine (65% in hydrofluoric acid), THF, rt, 18 h, 32~87%.

Scheme 6. Regents and conditions: (a) $NaNO_2$, HCl, H_2O, 0 ^oC, 0.5 h; (b) NaN_3, 0 ^oC to rt, 4.5 h, 24~97% in two steps; (c) **41**, $CuSO_4$, L-ascorbic acid sodium salt, CH_3OH-H_2O, 35~40 ^oC, 48 h, 31~90%; (d) $LiAlH_4$, THF, 0 ^oC, 1 h, 45~94%; (e) PBr_3, DCM, rt, overnight, 47~81%; (f) **45** or **47**, NaH, THF, 0 ^oC to rt, overnight, 41~79%; (g) 25% $NH_3 \cdot H_2O$, rt, 3 h, 19~87%.

Scheme 7. Regents and conditions: (a) $NaNO_2$, HCl, H_2O, 0 ^oC, 0.5 h; (b) NaN_3, 0 ^oC to rt, 4.5 h; (c)

1 tert-butyl nitrite, CH_3CN, rt, 92%.

Fig. 1

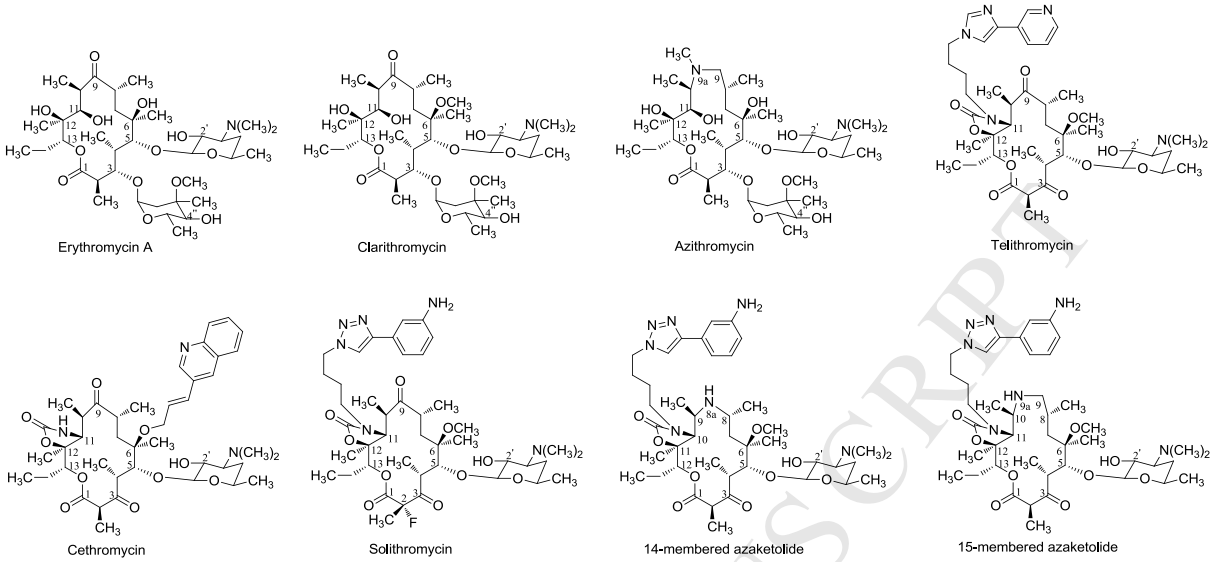
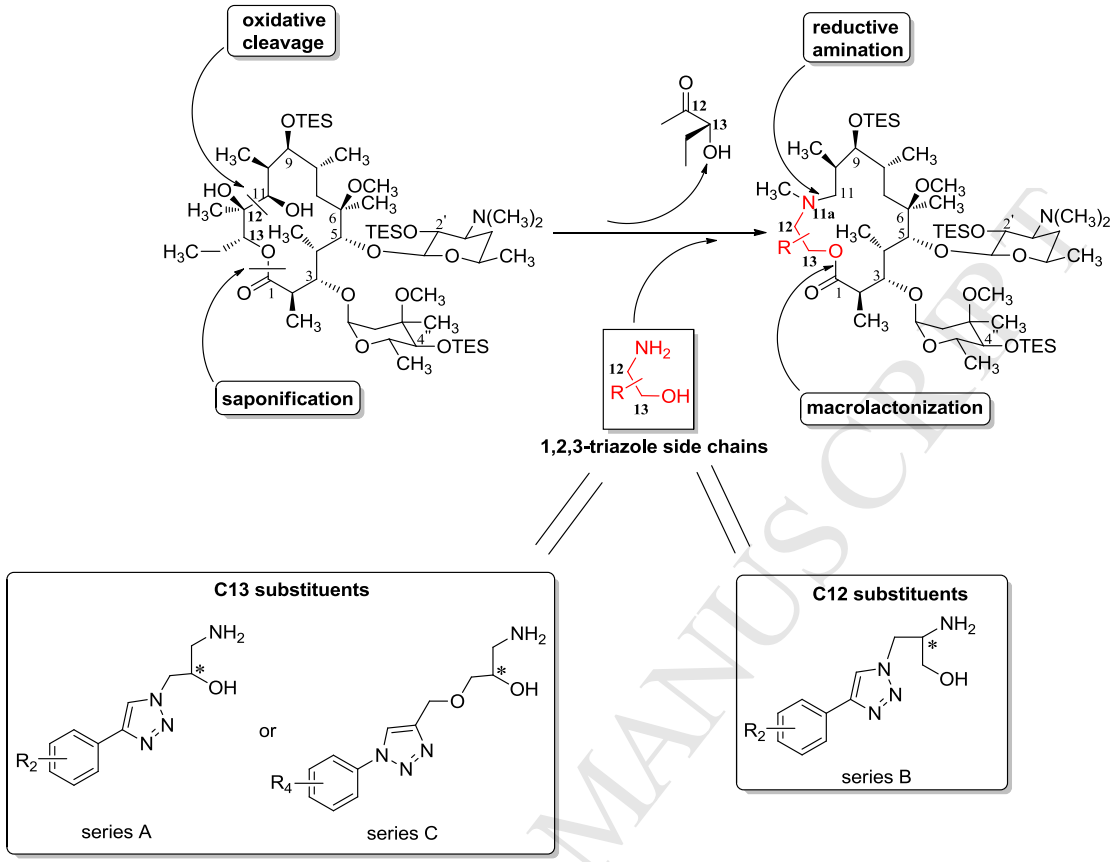
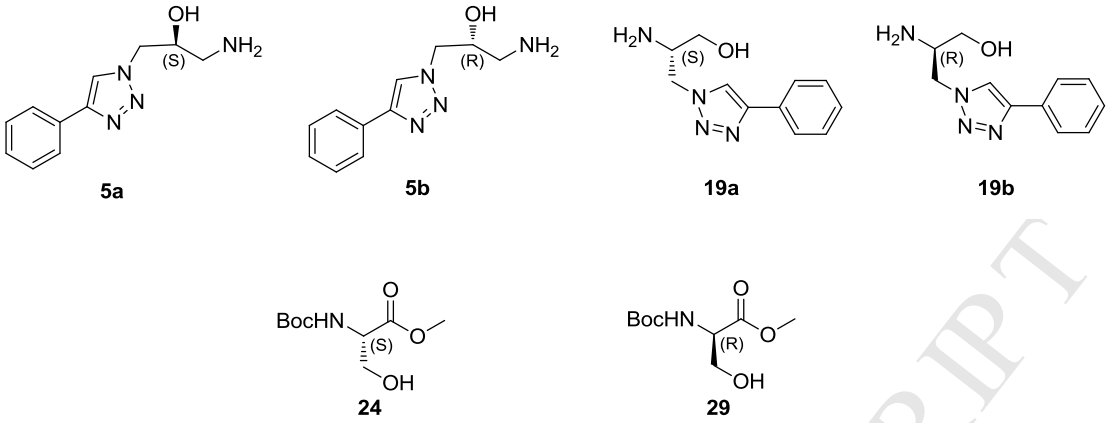


Fig. 2



1 **Fig. 3**



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3

4

Fig. 4

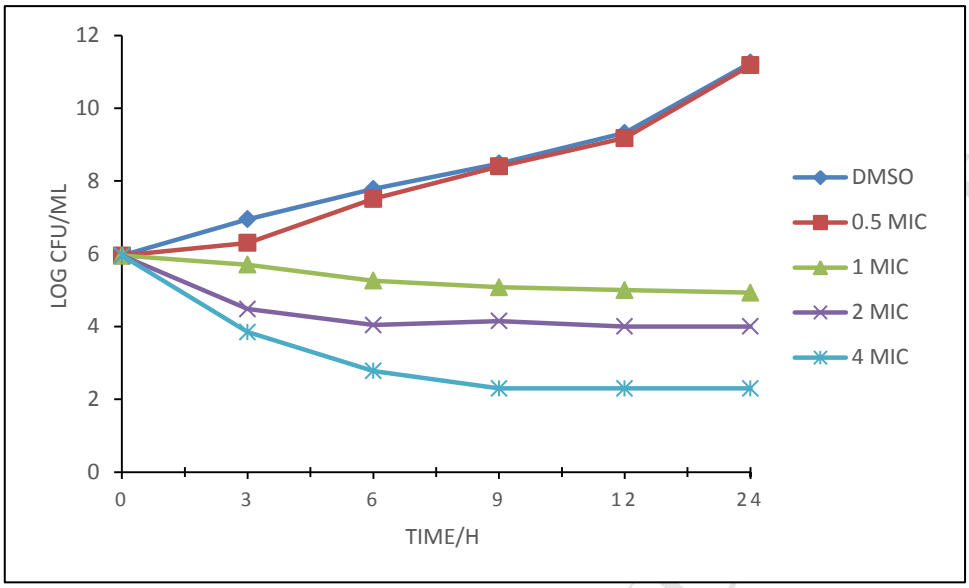
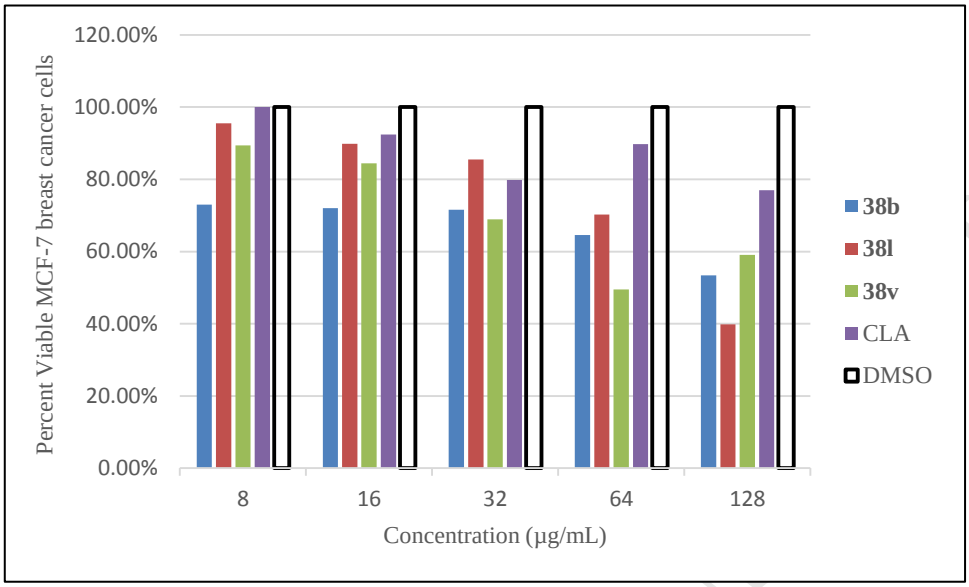
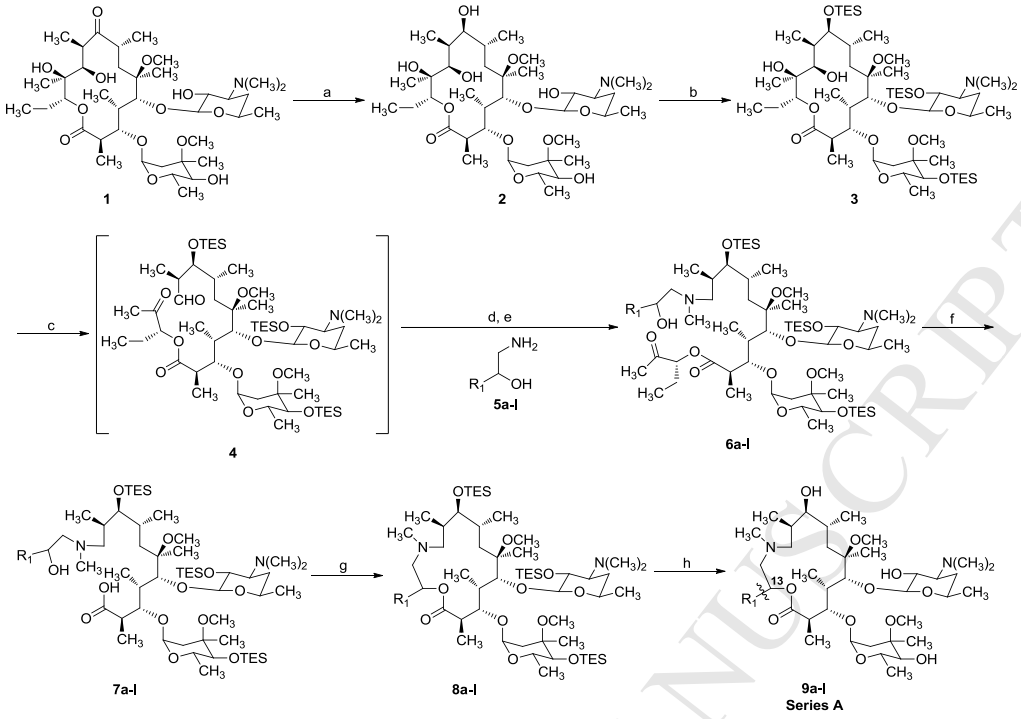
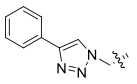
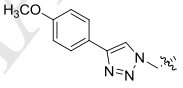
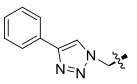
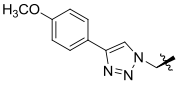
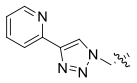
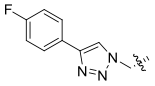
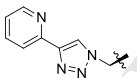
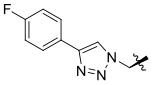
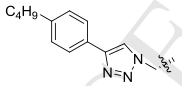
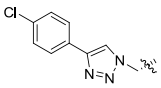
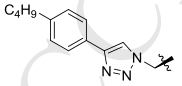
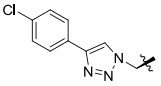


Fig. 5

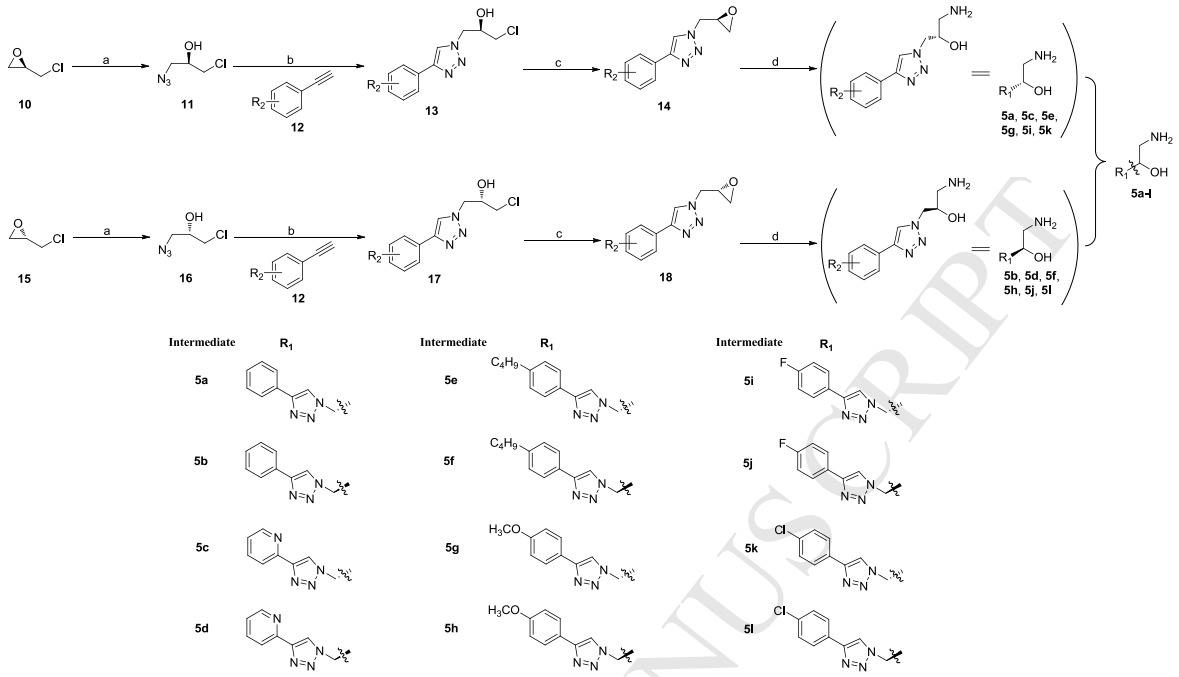


Scheme 1

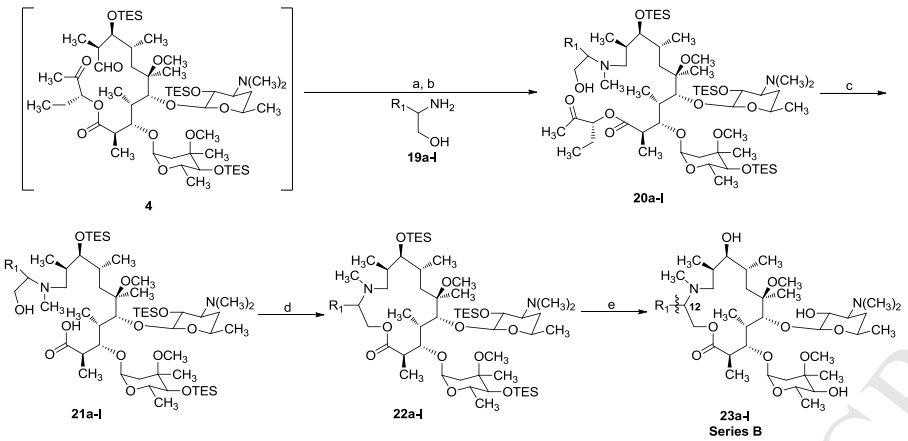


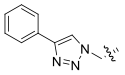
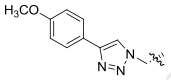
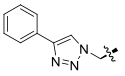
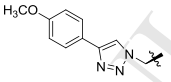
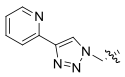
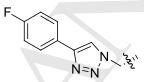
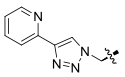
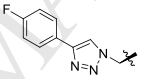
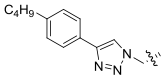
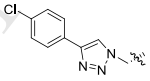
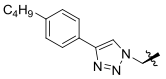
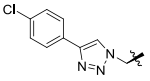
Compound	R_1	Configuration of C13	Compound	R_1	Configuration of C13
9a		**S**	**9g**		**S**
9b		**R**	**9h**		**R**
9c		**S**	**9i**		**S**
9d		**R**	**9j**		**R**
9e		**S**	**9k**		**S**
9f		**R**	**9l**		**R**

Scheme 2

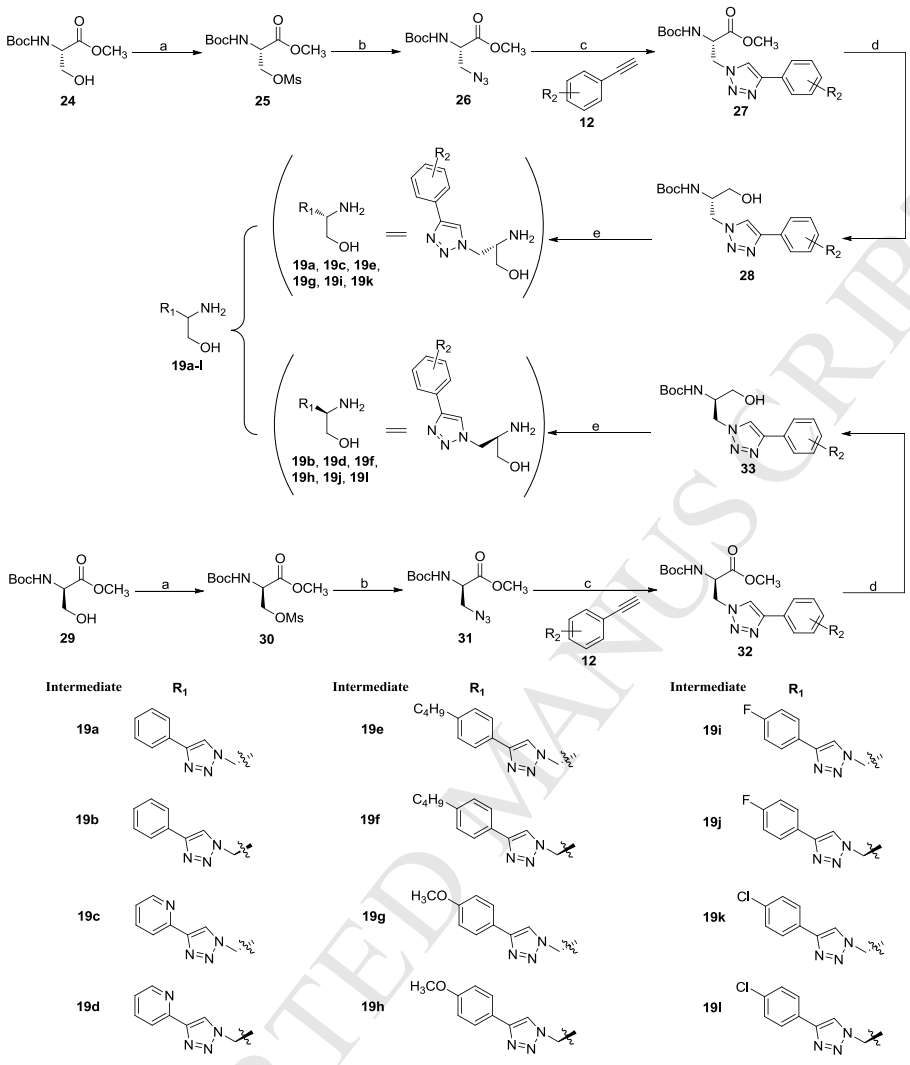


Scheme 3



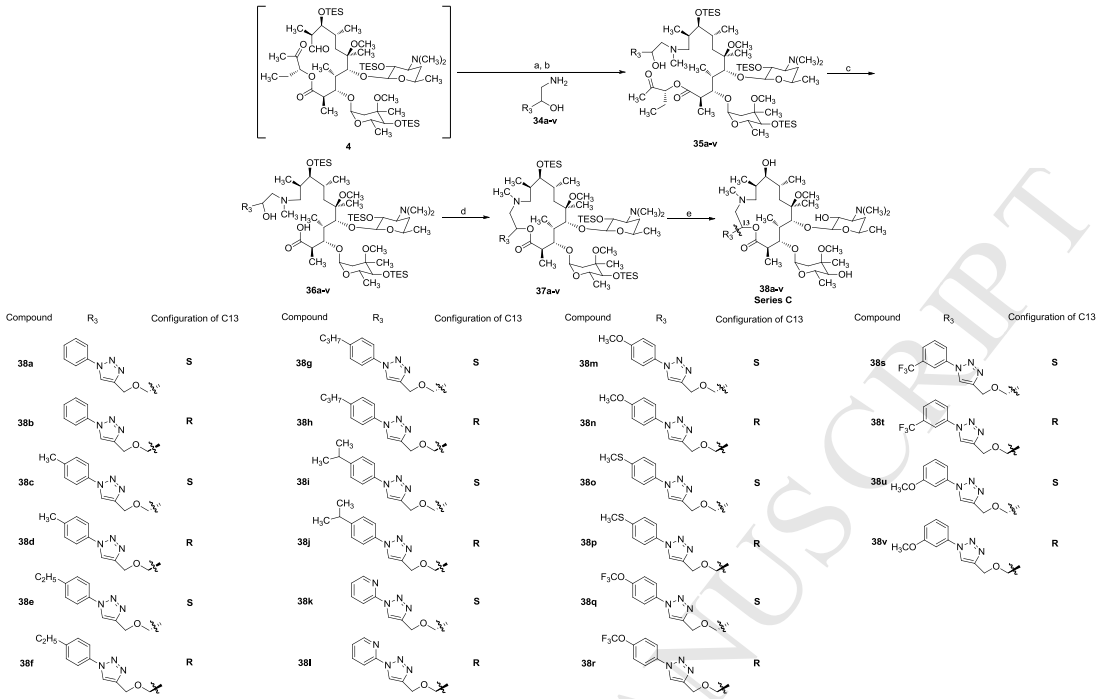
Compound	R_1	Configuration of C12	Compound	R_1	Configuration of C12
23a		**S**	**23g**		**S**
23b		**R**	**23h**		**R**
23c		**S**	**23i**		**S**
23d		**R**	**23j**		**R**
23e		**S**	**23k**		**S**
23f		**R**	**23l**		**R**

Scheme 4



Intermediate	R_1	Intermediate	R_1	Intermediate	R_1
19a		19e		19i	
19b		19f		19j	
19c		19g		19k	
19d		19h		19l	

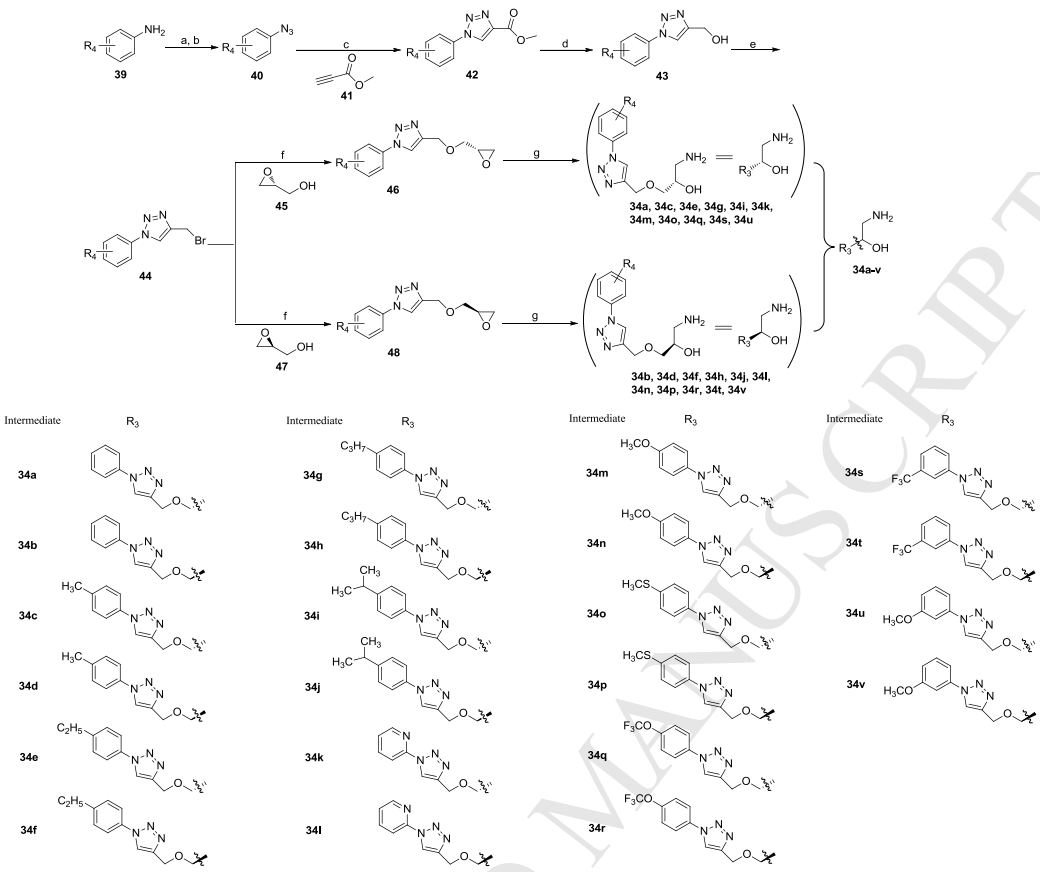
Scheme 5



Compound	R_3	Configuration of C13
38a		S
38b		R
38c		S
38d		R
38e		S
38f		R
38g		S
38h		R
38i		S
38j		R
38k		S
38l		R
38m		S
38n		R
38o		S
38p		R
38q		S
38r		R
38s		S
38t		R
38u		S
38v		R

1 **Scheme 6**

2



3

Scheme 7

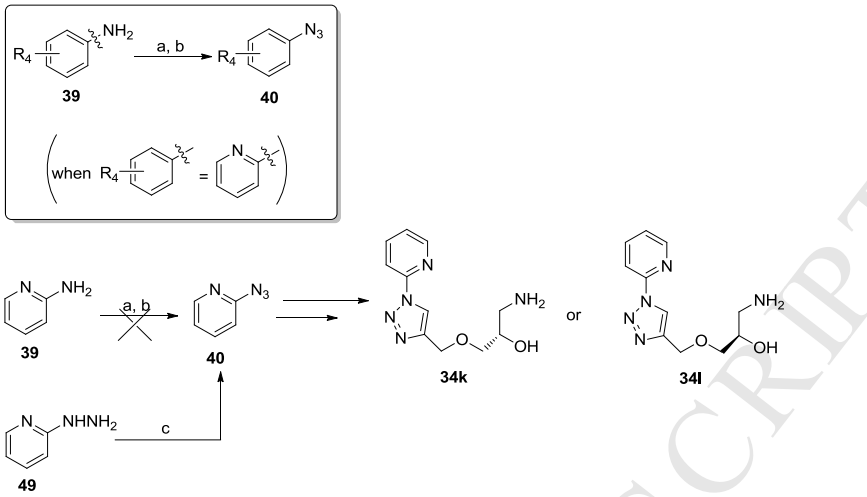
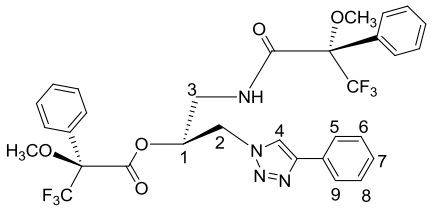


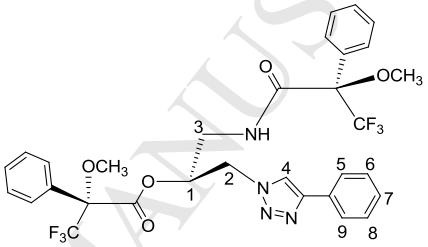
Table 1

^{1}H NMR spectral data of diastereomeric MTPA esters of **5a** (δ, C_5D_5N)

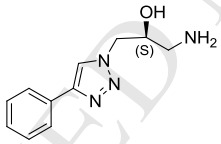
No.	(S)-MTPA ester **50**	(R)-MTPA ester **51**	Δδ
1	5.27 – 5.22 (m, 1H)	5.25 – 5.21 (m, 1H)	0.02
2	5.09 (dd, J = 13.9, 4.2 Hz, 1H)	5.04 (dd, J = 13.9, 4.3 Hz, 1H)	0.05
	4.96 (dd, J = 13.9, 7.1 Hz, 1H)	4.92 (dd, J = 13.9, 7.0 Hz, 1H)	0.04
3	3.86 – 3.83 (m, 1H)	3.80 – 3.78 (m, 1H)	0.06
	3.56 – 3.53 (m, 1H)	3.52 – 3.48 (m, 1H)	0.04
4-9	8.04 – 8.03 (m, 6H)	8.06 – 8.03 (m, 6H)	-0.02



(S)-MTPA ester **50**



(R)-MTPA ester **51**



5a

Table 2

In vitro antibacterial activity of the series A (**9a-9l**)

Compound	Minimum inhibitory concentration / MIC (μg/mL)									
	S. aureus ATCC25923[a]	*S. pyogenes* 1[b]	*E. coli* ATCC25922[c]	*P. aeruginosa* ATCC27853[d]	*B. subtilis* ATCC9372[e]	*S. aureus* ATCC31007[f]	*S. aureus* ATCC43300[g]	*S. pneumoniae* B1[h]	*S. pneumoniae* AB11[i]	*S. pyogenes* 2[j]
9a	0.5	0.5	64	64	1	128	256	64	64	64
9b	1	0.12	32	64	1	256	256	256	128	128
9c	2	1	128	64	4	>256	>256	128	128	128
9d	4	1	128	64	2	>256	>256	>256	256	128
9e	8	8	>128	>128	32	8	8	64	8	8
9f	1	0.06	128	64	1	32	16	16	32	16
9g	32	4	>128	>128	64	256	256	256	128	64
9h	1	0.12	32	64	1	>256	>256	>256	256	128
9i	0.5	0.25	32	32	0.5	128	128	64	16	64
9j	2	0.25	32	64	2	256	256	256	256	64
9k	8	2	128	>128	16	64	64	64	64	32
9l	2	0.12	32	64	1	128	128	128	128	64
AZM	≤0.25	≤0.03	64	16	≤0.25	>256	>256	>256	256	256
CAM	≤0.25	≤0.03	128	32	≤0.25	>256	>256	>256	128	256

[a]*S. aureus* ATCC25923: *Staphylococcus aureus* ATCC25923, erythromycin-susceptible strain;

[b]*S. pyogenes* 1: *Streptococcus pyogenes* 1, erythromycin-susceptible strain isolated clinically;

[c]*E. coli* ATCC25922: *Escherichia coli* ATCC25922, penicillin-susceptible strain;

[d]*P. aeruginosa* ATCC27853: *Pseudomonas aeruginosa* ATCC27853, penicillin-susceptible strain, not characterized;

[e]*B. subtilis* ATCC9372; *Bacillus subtilis* ATCC9372, penicillin-susceptible strain;

[f]*S. aureus* ATCC31007: *Staphylococcus aureus* ATCC31007, penicillin-resistant strain;

[g]*S. aureus* ATCC43300: *Staphylococcus aureus* ATCC43300, methicillin-resistant strain;

[h]*S. pneumonia* B1: *Streptococcus pneumoniae* B1, erythromycin-resistant strain expressing the *erm*B gene;

[i]*S. pneumoniae* AB11: *Streptococcus pneumoniae* AB11, erythromycin-resistant strain expressing the *erm*B and *mef*A genes;

[j]*S. pyogenes* 2: *Streptococcus pyogenes* 2, erythromycin-resistant strain isolated clinically.

Table 3

In vitro antibacterial activity of the series B (**23a**-**23l**)

Compound	Minimum inhibitory concentration / MIC (μg/mL)									
	S. aureus ATCC25923[a]	*S. pyogenes* 1[b]	*E. coli* ATCC25922[c]	*P. aeruginosa* ATCC27853[d]	*B. subtilis* ATCC9372[e]	*S. aureus* ATCC31007[f]	*S. aureus* ATCC43300[g]	*S. pneumoniae* B1[h]	*S. pneumoniae* AB11[i]	*S. pyogenes* 2[j]
23a	32	2	>128	>128	16	256	256	256	128	128
23b	8	8	64	64	16	128	256	256	256	128
23c	64	16	>128	>128	32	>256	>256	>256	256	256
23d	16	4	64	64	32	256	256	256	128	256
24e	16	4	>128	>128	8	16	>256	>256	16	16
23f	128	16	128	>128	32	64	128	64	64	16
23g	64	4	>128	>128	32	256	256	256	64	256
23h	64	4	>128	>128	32	32	128	128	128	128
23i	64	16	>128	>128	32	128	128	256	128	128
23j	16	16	>128	128	16	128	256	128	128	128
23k	32	16	>128	>128	16	128	64	256	128	64
23l	8	8	>128	>128	8	64	64	64	64	32
AZM	≤0.25	≤0.03	64	16	≤0.25	>256	>256	>256	256	256
CAM	≤0.25	≤0.03	128	32	≤0.25	>256	>256	>256	128	256

[a]*S. aureus* ATCC25923: *Staphylococcus aureus* ATCC25923, erythromycin-susceptible strain;

[b]*S. pyogenes* 1: *Streptococcus pyogenes* 1, erythromycin-susceptible strain isolated clinically;

[c]*E. coli* ATCC25922: *Escherichia coli* ATCC25922, penicillin-susceptible strain;

[d]*P. aeruginosa* ATCC27853: *Pseudomonas aeruginosa* ATCC27853, penicillin-susceptible strain, not characterized;

[e]*B. subtilis* ATCC9372; *Bacillus subtilis* ATCC9372, penicillin-susceptible strain;

[f]*S. aureus* ATCC31007: *Staphylococcus aureus* ATCC31007, penicillin-resistant strain;

[g]*S. aureus* ATCC43300: *Staphylococcus aureus* ATCC43300, methicillin-resistant strain;

[h]*S. pneumonia* B1: *Streptococcus pneumoniae* B1, erythromycin-resistant strain expressing the *erm*B gene;

[i]*S. pneumoniae* AB11: *Streptococcus pneumoniae* AB11, erythromycin-resistant strain expressing the *erm*B and *mef*A genes;

[j]*S. pyogenes* 2: *Streptococcus pyogenes* 2, erythromycin-resistant strain isolated clinically.

Table 4

In vitro antibacterial activity of the series C (**38a**-**38v**)

Compound	Minimum inhibitory concentration / MIC (μg/mL)									
	S. aureus ATCC25923[a]	*S. pyogenes* 1[b]	*E. coli* ATCC25922[c]	*P. aeruginosa* ATCC27853[d]	*B. subtilis* ATCC9372[e]	*S. aureus* ATCC31007[f]	*S. aureus* ATCC43300[g]	*S. pneumoniae* B1[h]	*S. pneumoniae* AB11[i]	*S. pyogenes* 2[j]
38a	1	1	128	128	1	>256	256	256	64	64
38b	≤0.25	0.25	64	16	≤0.25	>256	>256	>256	128	128
38c	4	4	128	128	2	256	128	128	64	32
38d	0.5	1	64	16	≤0.25	256	256	256	64	64
38e	4	4	128	128	2	64	64	32	32	32
38f	0.5	0.5	64	16	≤0.25	128	128	128	32	64
38g	4	4	64	>128	1	32	16	16	8	32
38h	0.5	1	64	16	0.5	128	128	64	32	64
38i	4	4	64	128	1	32	32	16	16	16
38j	1	1	64	16	0.5	128	64	64	32	32
38k	2	2	128	128	0.5	>256	>256	>256	128	128
38l	≤0.25	0.5	64	16	≤0.25	>256	>256	>256	128	128
38m	8	4	128	128	2	256	256	256	128	128
38n	1	0.25	64	16	0.5	>256	>256	>256	64	128
38o	4	4	128	128	2	128	64	64	32	32
38p	1	2	64	16	0.5	256	256	256	64	64
38q	4	4	128	>128	2	64	32	32	16	32
38r	2	2	64	16	1	128	128	128	32	32
38s	8	4	128	>128	2	64	32	32	16	32

38t	1	2	64	16	1	256	256	128	64	64
38u	2	2	128	128	2	256	256	128	64	64
38v	≤0.25	0.5	64	32	≤0.25	>256	>256	>256	128	128
AZM	≤0.25	≤0.03	64	16	≤0.25	>256	>256	>256	256	256
CAM	≤0.25	≤0.03	128	32	≤0.25	>256	>256	>256	128	256

[a]*S. aureus* ATCC25923: *Staphylococcus aureus* ATCC25923, erythromycin-susceptible strain;

[b]*S. pyogenes* 1: *Streptococcus pyogenes* 1, erythromycin-susceptible strain isolated clinically;

[c]*E. coli* ATCC25922: *Escherichia coli* ATCC25922, penicillin-susceptible strain;

[d]*P. aeruginosa* ATCC27853: *Pseudomonas aeruginosa* ATCC27853, penicillin-susceptible strain, not characterized;

[e]*B. subtilis* ATCC9372; *Bacillus subtilis* ATCC9372, penicillin-susceptible strain;

[f]*S. aureus* ATCC31007: *Staphylococcus aureus* ATCC31007, penicillin-resistant strain;

[g]*S. aureus* ATCC43300: *Staphylococcus aureus* ATCC43300, methicillin-resistant strain;

[h]*S. pneumonia* B1: *Streptococcus pneumoniae* B1, erythromycin-resistant strain expressing the *erm*B gene;

[i]*S. pneumoniae* AB11: *Streptococcus pneumoniae* AB11, erythromycin-resistant strain expressing the *erm*B and *mef*A genes;

[j]*S. pyogenes* 2: *Streptococcus pyogenes* 2, erythromycin-resistant strain isolated clinically.

Table 5

Comparison of MIC and MBC values for promising compounds **38b**, **38l**, **38v**, **9e** and **38g** in *S. aureus* ATCC25923 and *S. pneumoniae* AB11

Compound	MBC (μg/mL)	MIC (μg/mL)	MBC/MIC
		S. aureus ATCC25923[a]	
38b	128	≤0.25	≥512
38l	>128	≤0.25	>512
38v	>128	≤0.25	>512
CAM	128	≤0.25	≥512
		S. pneumoniae AB11[b]	
9e	64	8	8
38g	64	8	8
CAM	128	128	1

[a]*S. aureus* ATCC25923: *Staphylococcus aureus* ATCC25923: erythromycin-susceptible strain;

[b]*S. pneumoniae* AB11: *Streptococcus pneumoniae* AB11: erythromycin-resistant strain expressing the *erm*B and *mef*A genes.

Highlights

> Three series of 11a-azahomoclarithromycin derivatives were designed and synthesized > They were evaluated for their biological activities > **9e** had the most potent activity against resistant bacteria > **38b** had the most potent activity against sensitive bacteria > The SARs of 11a-azahomoclarithromycin derivatives were illuminated in detail.

Graphical Abstract:

Design, synthesis and antibacterial evaluation of novel 15-membered 11a-azahomoclarithromycin derivatives with the 1, 2, 3-triazole side chain

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