Bioorganic Chemistry 113 (2021) 104992

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Design, synthesis and structure–activity relationships of novel N11-, C12- and C13-substituted 15-membered homo-aza-clarithromycin derivatives against various resistant bacteria

Yinhui Qin, Di Song, Yuetai Teng, Xingbang Liu, Panpan Zhang, Nan Zhang, Na Zhang, Weijin Chen, Shutao Ma *

Department of Medicinal Chemistry, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University, 44 West Wenhua Road, Jinan 250012, PR China

ARTICLE INFO

Keywords:
Homo-aza-clarithromycin derivatives
Synthesis
Antibacterial activity
Structure-activity relationships

ABSTRACT

Bacterial infections are still the main significant problem of public health in the world, and their elimination will greatly rely on the discovery of antibacterial drugs. In the processes of our searching for novel macrolide derivatives with excellent activity against sensitive and resistant bacteria, three series of novel N11-, C12- and C13-substituted 15-membered homo-aza-clarithromycin derivatives were designed and synthesized as Series A, B and C by creatively opening the lactone ring of clarithromycin (CAM), introducing various 4-substituted phenyl-1*H*-1,2,3-triazole side chains at the N11, C12 or C13 position of CAM and macrolactonization. The results from their *in vitro* antibacterial activity demonstrated that compounds **20c**, **20d** and **20f** displayed not only the most potent activity against *S. aureus* ATCC25923 with the MIC values of 0.5, 0.5 and 0.5 μg/mL, but also greatly improved activity against *B. subtilis* ATCC9372 with the MIC values of less than or equal to 0.25, 0.25 and 0.25 μg/mL, respectively. In particular, compound **11g** exhibited the strongest antibacterial effectiveness against all the tested resistant bacterial strains and had well balanced activity with the MIC values of 4–8 μg/mL. Further study on minimum bactericidal concentration and kinetics confirmed that compound **11g** possessed a bacteriostatic effect on bacterial proliferation. Moreover, the results of molecular docking revealed an potential additional binding force between compound **11g** and U790 in addition to the normal binding force of macrolide skeleton, which may explain why this compound performed the most potent activity against resistant bacteria. The results of cytotoxic assay indicated that compounds **20c**, **20d** and **20f** were non-toxic to human breast cancer MCF-7 cells at its effective antibacterial concentration.

1. Introduction

Development of potent antibacterial agents is a permanently new and unremitting investigation in the therapeutic field. Still, researchers want to find the best antibacterial agent. Recently, some novel heterocyclic compounds such as pyranopyrazoles, tri-substituted pyrazole, dihydropyridines and bis(indolyl)methanes derivatives were designed and synthesized and evaluated for their biological activities. The results showed that representative compounds exhibited not only significantly potent antibacterial activity against *Bacillus subtilis* ATCC6633, *Escherichia coli* ATCC8739 and *Proteus vulgaris* ATCC29213, but also excellent antifungal activity against *Aspergillus niger* MTCC1881 [1–5]. More importantly, macrolide antibiotics have always been a hot antibacterial field for scientists.

Macrolide antibiotics produced by *Streptomyces*, are a kind of weak alkaline compounds which contain a fourteen or sixteen-membered lactone ring. They have similar antibacterial spectrum and activity without cross-resistance with other commonly used antibiotics. Thus, macrolide antibiotics have become one of the most widely used oral antibacterial drugs in the field of anti-infective therapy [6]. Erythromycin (Fig. 1) is the first macrolide antibiotic, which was approved by the US Food and Drug Administration for the treatment of respiratory tract infections caused by Gram-positive bacteria in the 1950s [7]. Erythromycin has excellent antibacterial activity and low toxicity

* Corresponding author at: Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Shandong University, 44, West Culture Road, Jinan 250012, PR China.
E-mail address: mashutao@sdu.edu.cn (S. Ma).

https://doi.org/10.1016/j.bioorg.2021.104992
Received 13 February 2021; Received in revised form 12 April 2021; Accepted 11 May 2021
Available online 18 May 2021

clinically, but it is hindered by its narrow antibacterial spectrum and poor stability in gastric acid [8]. Thus, second generation macrolide antibiotics have been developed to overcome those shortcomings, which are semisynthetic derivatives of erythromycin, such as clarithromycin (CAM), azithromycin (AZM) and roxithromycin (Fig. 1). Their drug properties are more greatly enhanced than those of erythromycin, including higher acid stability, stronger antibacterial activity, wider antibacterial spectrum, better pharmacokinetic properties and fewer gastrointestinal side effects [9–12]. Consequently, these second generation macrolide antibiotics have replaced erythromycin as first-line treatment for respiratory tract infections, and especially, have played an important role in the treatment of mycoplasma and chlamydia pneumonia and soft tissue infections. However, with the widespread use of second generation macrolide antibiotics in clinical practice, some pathogens have gradually developed resistance to them, which has brought great difficulties to the treatment of the above infectious diseases. Thus, it is imperative to strengthen the exploration of new generation of macrolide antibiotics [13]. Telithromycin, cethromycin and solithromycin (Fig. 1) are the representative drugs of third generation macrolide antibiotics, which exhibit excellent antibacterial activity against methicillin-resistant *Staphylococcus aureus* and multi-drug resistant *Streptococcus pneumoniae* [14–16]. In particular, their antibacterial activity against erythromycin-resistant bacteria is much stronger than that of the first two generations of macrolide antibiotics [17,18], which is attributed to their aralkyl side chains in structure, enhancing the binding force of the third generation macrolide antibiotics for ribosomes of resistant bacteria [19–23]. With their increasing clinical application, third generation macrolide antibiotics still face the serious problems of hepatotoxicity and bacterial resistance. Therefore, it is necessary to strive to discover newer chemical entities of macrolide antibiotics with potent activity against resistant bacteria.

In recent years, many new macrolide derivatives have been obtained by the structural modification of macrolides to improve antibacterial activity against various bacterial strains [24]. For instance, novel carbonate-triazole derivatives of AZM and *N*-alkylammonium bromides of AZM and CAM were designed, synthesized by Anna Janas et al. and their biological studies revealed potential antibacterial activity of quaternary *N*-alkylammonium bromides of CAM as compared to AZM [25]. It is reported that macrolide derivatives provided by structural modifications at the C13 position of erythromycin are very active against resistant bacteria [26,27]. However, these modifications are blocked by the lack of chemical reaction activity at the C13 position. Nevertheless, researchers have been trying their best to overcome these difficulties and have made positive progress. For example, the methods for macrolactone skeleton reconstruction have been established by Tomoaki Miura [28] and Tomohiro Sugimoto [29].

In order to find new macrolide derivatives with novel macrolactone skeletons, 15-membered 11a-homo-aza-clarithromycin derivatives were designed and synthesized using the above synthetic methods in our previous study. Among which, some derivatives exhibited excellent antibacterial activity against sensitive bacteria [30]. For example, **38b$_{pre}$**, **38l$_{pre}$** and **38v$_{pre}$** displayed the strongest activity against *S. aureus* ATCC25923 and *Bacillus subtilis* ATCC9372 with the minimum inhibitory concentration (MIC) values 0.25 μg/mL, which were better than the others, and also better than (or equal to) CAM. Moreover, the antibacterial activity of **38d$_{pre}$** and **38f$_{pre}$** against most sensitive bacteria was comparable to that of CAM. For instance, they exhibited excellent antibacterial activity against *B. subtilis* ATCC9372 with an MIC value of 0.25 μg/mL. As for the activity against the four resistant bacteria strains of *S. aureus* ATCC31007, *S. aureus* ATCC43300, *S. pneumoniae* AB11 and *S. pyogenes* 2, **9e$_{pre}$** (Fig. 2), which is C13 substituted 15-membered 11a-homo-aza-clarithromycin derivative with 4-butylphenyl-1*H*-1,2,3-triazole linked to the C13 position of the 15-membered lactone by a methylene, displayed 16–32 fold improvement over CAM. **23e$_{pre}$** showed greatly improved activity against *S. aureus* ATCC31007, *S. pneumoniae* AB11 and *S. pyogenes* 2, which is C12 substituted 15-membered 11a-homo-aza-clarithromycin, possessing the same side chain at the C12 position of the 15-membered lactone to **9e$_{pre}$**. However, the replacement of *n*-butyl group at benzene ring by other groups resulted in poor antibacterial activity.

The computational analyses of **9e$_{pre}$** and CAM with the crystal structure of the *Escherichia coli* ribosome (PDB code: 4V7S [31]) by

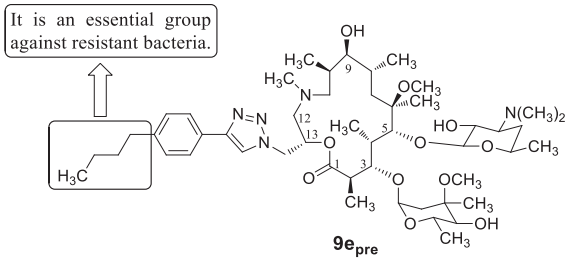


Fig. 2. Structure of compound **9e$_{pre}$** and its essential group against resistant bacteria.

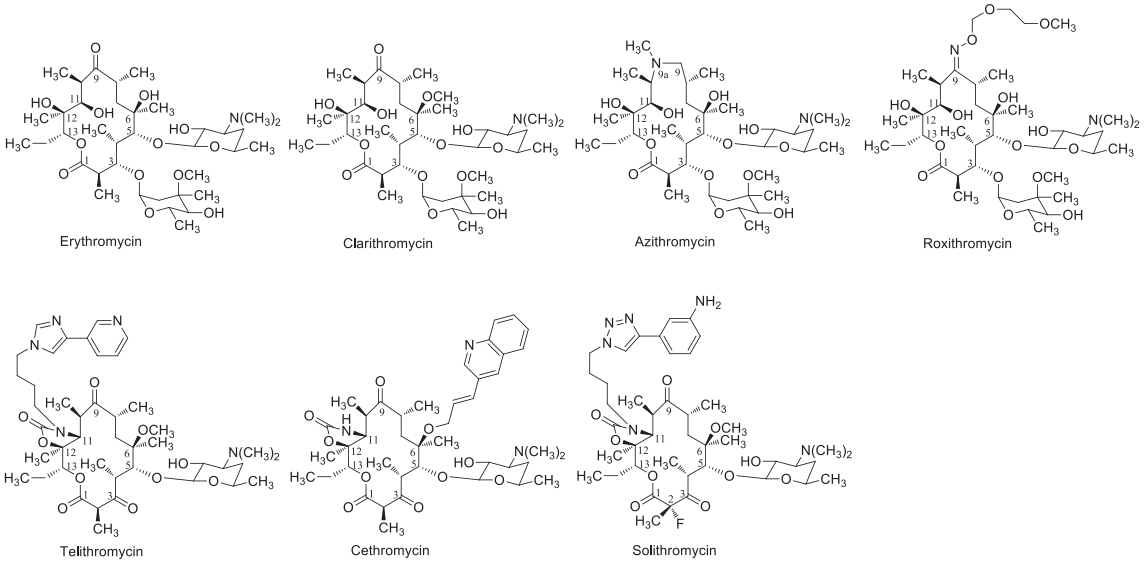


Fig. 1. Structures of representative macrolides.

autodock indicated that the 4-*n*-butylphenyl-1*H*-1,2,3-triazole side chain can extend to the bacterial ribosomal nucleotide residue U790, may generate π-π stacking, electrostatic or hydrophobic interaction with U2609, A752 and U790 (Fig. 3**a**) [19,32]. There is a strong hydrogen bond interaction of the 4′'–OH of **9e**$_{pre}$ and G2505. In addition, the conformation of 15-membered macrolactone skeleton has a certain degree of change compared with that of CAM (Fig. 3**b**). In particular, the 4-*n*-butylphenyl-1*H*-1,2,3-triazole side chain at the C13 position may produce additional hydrophobic interaction with U790 in the binding site of the ribosome, leading to dramatically increased activity against resistant bacteria strains.

The above findings encourage us continue to explore the effects of introducing 4-*n*-butylphenyl-1*H*-1,2,3-triazole side chains into other positions of 15-membered macrolactone skeleton, such as N11 position, on activity against resistant bacteria. Thus, N11-substituted 15-membered homoclarithromycin derivatives (Series A) were designed and synthesized by introduction of 4-alkylphenyl-1*H*-1,2,3-triazole side chains into the N11 position of 15-membered macrolactone skeleton (Fig. 4). The design ideas of Series A are as follows: (1) Changing the length (extension or shortening) and types (non-oxygen-containing or oxygen-containing alkyl group, and branched or straight alkyl group, etc.) of the alkyl group on the benzene ring, which may approach U790 of 23S rRNA in bacterial ribosome and produce stronger π-π stacking, electrostatic or hydrophobic interaction with it; (2) Altering position of introduced 4-alkyllphenyl-1*H*-1,2,3-triazole side chain is to generate stronger π-π stacking, electrostatic or hydrophobic interaction with U790; (3) Besides, the 2′-OH of 15-membered macrolactone skeleton may still bind to A2058 and A2059 of 23S rRNA of bacterial ribosome well, producing activity against sensitive bacteria [33].

In our previous study [30], only **9e**$_{pre}$ and **9f**$_{pre}$ with 4-alkyllphenyl-1*H*-1,2,3-triazole side chains at the C13 position, and **23e**$_{pre}$ and **23f**$_{pre}$ with 4-alkyllphenyl-1*H*-1,2,3-triazole side chains at the C12 position were explored. However, it is still unclear how the length (extension or shortening) and types (non-oxygen-containing or oxygen-containing alkyl groups, and branched or straight alkyl group, etc.) of the alkyl group on the benzene ring affect activity against sensitive and resistant and bacteria. In addition, the effect of the configuration (*R* or *S*) of C13 and C12 on antibacterial activity was further investigated. In order to clarify the above problems, C13-substituted 15-membered homo-aza-clarithromycin derivatives (Series B) and C12-substituted 15-membered homo-aza-clarithromycin derivatives (Series C) were designed and synthesized through opening of CAM lactone ring, introduction of 4-alkylphenyl-1*H*-1,2,3-triazole side chains into the C13 position and the C12 position, and macrolactonization (Fig. 5). In fact, in addition to the different introduction position and extension direction of 4-alkylphenyl-1*H*-1,2,3-triazole side chains, the design ideas of Series B and C are similar to that of Series A, which are to explore the possible secondary force produced by the introduced side chain and nucleotide binding sites of 23S rRNA.

2. Chemistry

2.1. Synthesis of N11-substituted 15-membered homo-aza-clarithromycin derivatives (Series A)

The synthetic route of N11-substituted 15-membered homo-aza-clarithromycin derivatives **11a-11 m** (Series A) from CAM **1** is shown in Scheme 1. CAM **1** was reduced in the presence of $NaBH_4$ to yield 9(*S*)-dihydroclarithromycin **2** [34], which was then subjected to selective protection of **2** with TESCl to give TES ether **3** [35]. After conversion of **3** into the corresponding acyclic aldehyde **4** through oxidation reaction, which was treated with ethanolamine **5** in the aid of $NaBH(OAc)_3$ to obtain the secondary amine **6**. Alkylation of **6** produced the corresponding tertiary amines **8a-8m** by reductive amination of the secondary amine with various substituted aldehydes **7a-7m** [36]. Saponification of the ester groups of **8a-8m** was carried out in the presence of the base catalyst LiOH to form carboxylic acids **9a-9m** in good yields. Macrocyclization [37] of **9a-9m** afforded TES-protected N11-substituted 15-membered homo-aza-clarithromycin derivatives **10a-10m**, which were followed by deprotection of the silane groups from **10a-10m** to provide the target compounds **11a-11m** (Series A).

Various substituted aldehydes **7a-7m** were prepared as key intermediates for the synthesis of Series A (Scheme 2). Conversion of 3-bromopropanol **12** into azide product **13** through substitution reaction with NaN_3 [38], which was followed by treatment with various substituted phenylacetylenes **14** to give the corresponding alcohols **15** [39]. Finally, **15** was oxidized with Dess-Martin periodinane to afford the desired aldehydes **7a-7m** in excellent yields [40].

2.2. Synthesis of C13-substituted 15-membered homo-aza-clarithromycin derivatives (Series B)

The 15-membered C13-substituted homo-aza-clarithromycin derivatives **20a-20l** (Scheme 3) were synthesized from **4** by using the similar cyclization process as previously described [30].

The synthetic route of intermediates **16a-16l** for the synthesis of

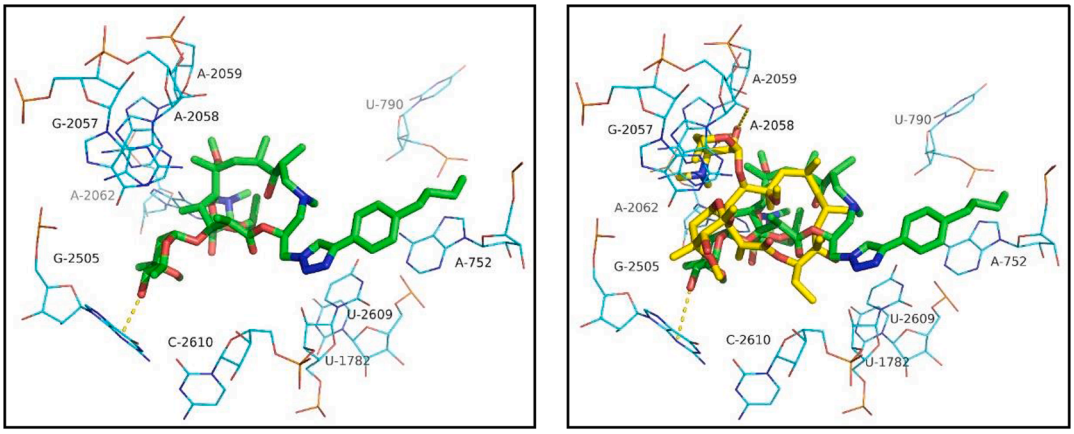


Fig. 3. (**a**) Model of compound **9e**$_{pre}$ docked into *E. coli* ribosome (PDB code: 4V7S [31]). In the model, the predicted hydrogen bonds between compound **9e**$_{pre}$ and the nucleotide residues are indicated by dotted lines; (**b**) The docking model of compound **9e**$_{pre}$ (green) and CAM (yellow) in *E. coli* ribosome. Both are located in approximately the same spatial area in *E. coli* ribosome. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

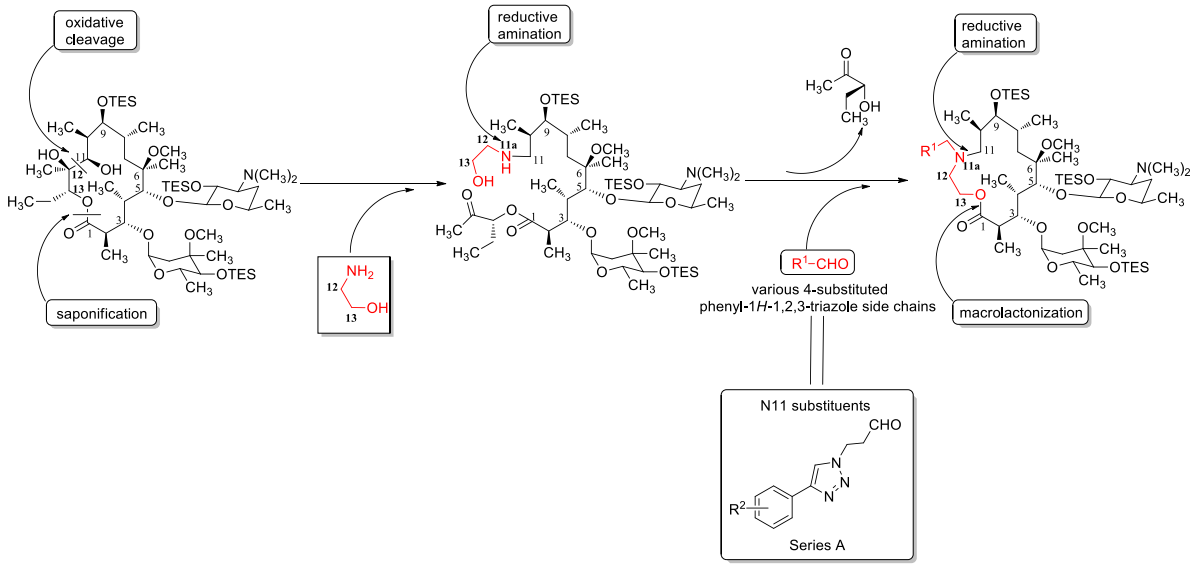


Fig. 4. Brief design strategy of Series A.

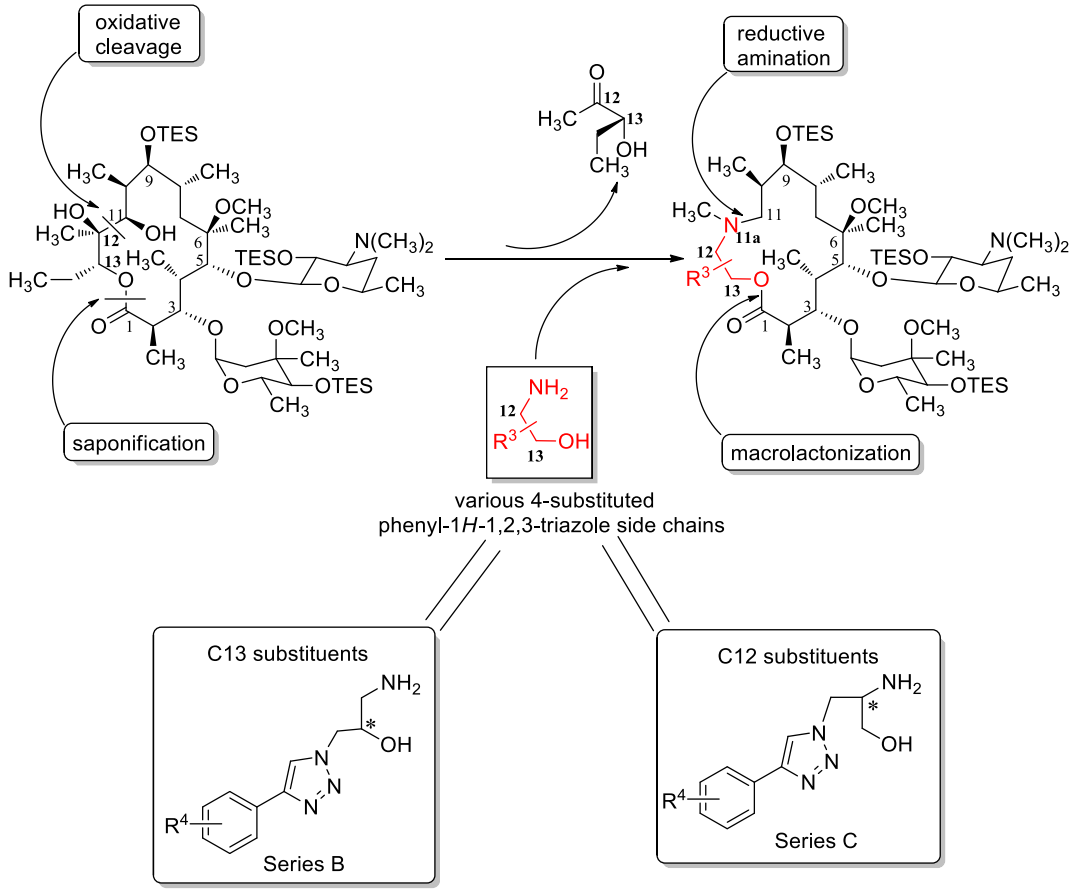
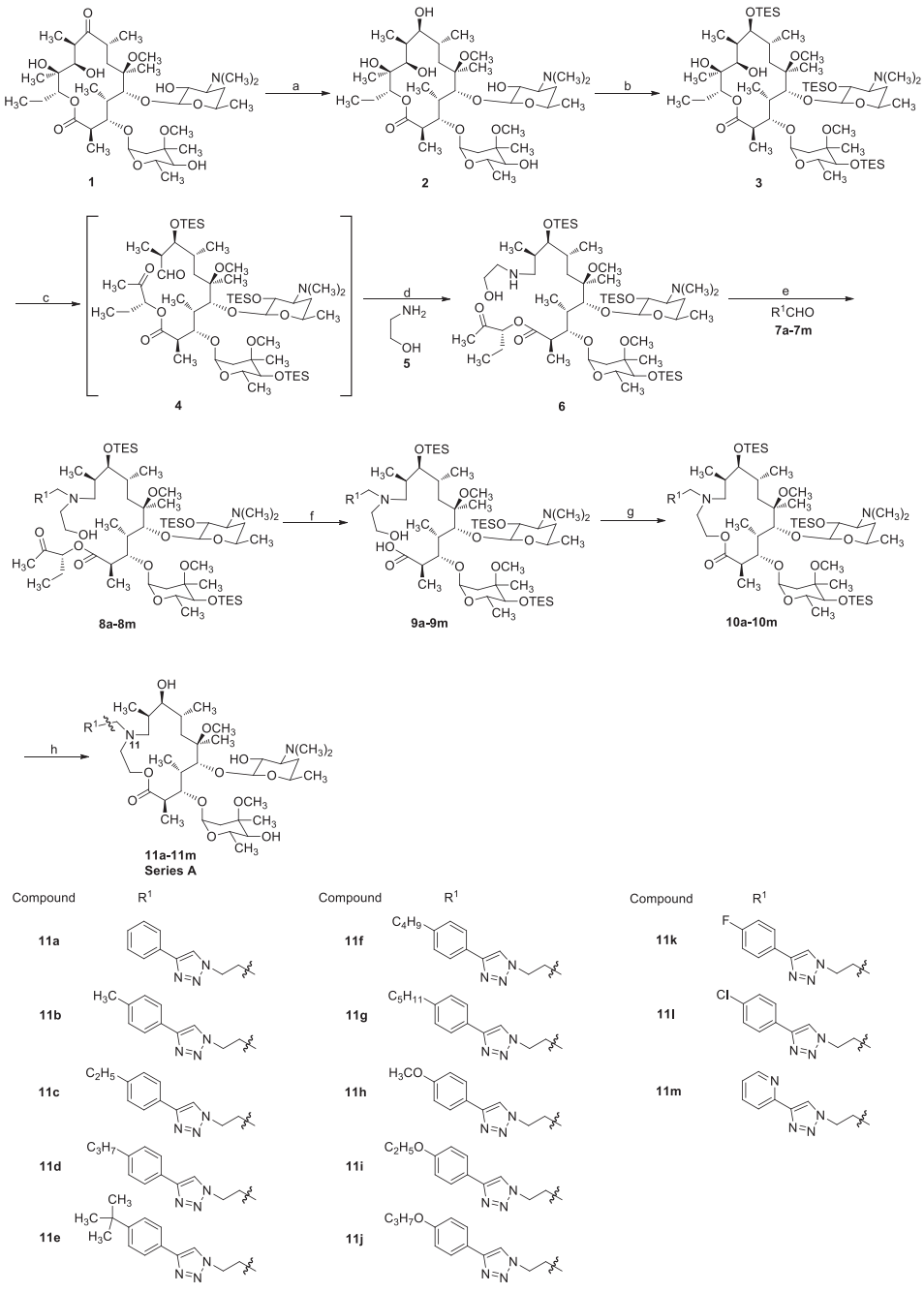


Fig. 5. Brief design of Series B and C.

Series B is shown in Scheme 4. Conversion of *R*-epichlorohydrin **21** into the corresponding azide **22** through azidation [41] was followed by treatment with corresponding substituted phenylacetylenes **23** with the aid of $CuSO_4$ and L-ascorbic acid sodium to afford chloroethanol **24** [39]. Epoxidation of **24** was carried out in the presence of NaOH to form the epoxide **25** [42], and subsequently, **25** was stereoselectively ring-opened to provide various substituted aminoalcohols **16a**, **16c**, **16e**, **16g**, **16i** and **16k** [35]. Their enantiomers **16b**, **16d**, **16f**, **16h**, **16j** and **16l** were also prepared from *S*-epichlorohydrin **26** by applying of the same synthetic method described above.



Scheme 1. Regents and conditions: (a) $NaBH_4$, CH_3OH-THF, rt, 24 h, 52%; (b) TESCl, imidazole, DMF, 0 °C to rt, 18 h, 68%; (c) $Pb(OAc)_4$, $CHCl_3$, 0 °C, 0.5 h; (d) **5**, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h, 72% in two steps from **3**; (e) **7a-7m**, $NaBH(OAc)_3$, $CHCl_3$, rt, 12 h; (f) LiOH, THF-C_2H_5OH-H_2O, rt, 6 h, 18–70% in two steps from **6**; (g) i) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, THF, rt, 4 h; ii) DMAP, CH_3CN, reflux, 0.5 h, 42–82%; (h) Hydrogen fluoride-pyridine (65% in hydrofluoric acid), THF, rt, 18 h, 32–80%.

2.3. Synthesis of C12-substituted 15-membered homo-aza-clarithromycin derivatives (Series C)

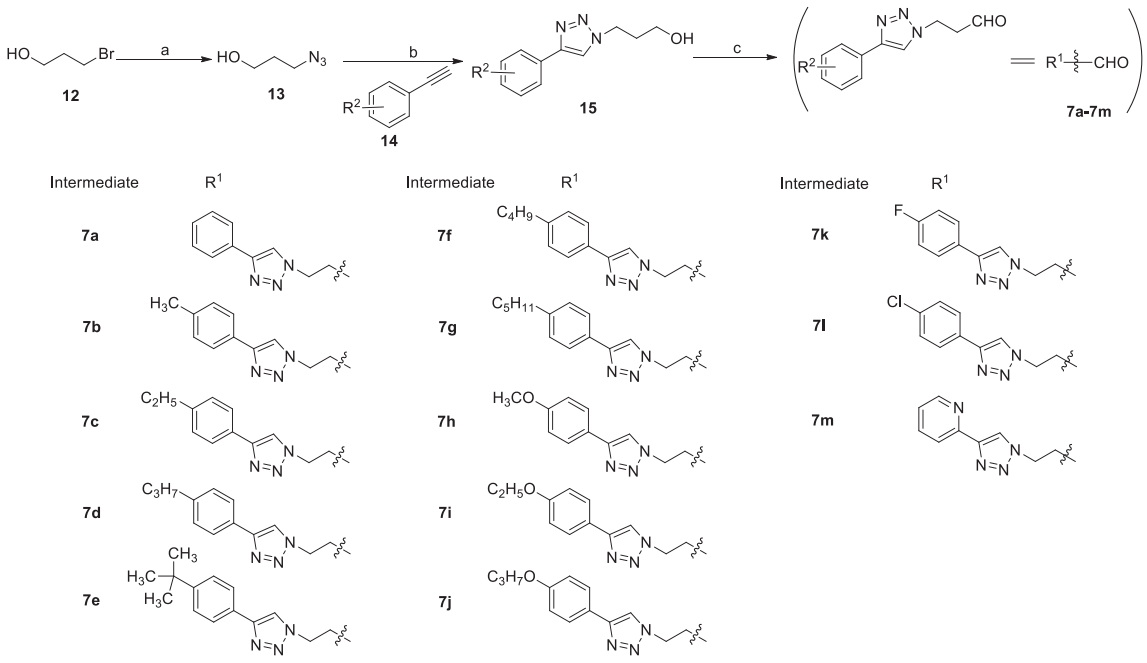
The 15-membered C12 substituted homo-aza-clarithromycin derivatives **34a-34l** (Scheme 5) were synthesized from **4** by using the similar cyclization process as previously described [30].

The synthetic route of intermediates **30a-30l** for the synthesis of Series C is outlined in Scheme 6. The Boc-L-serine methyl ester **35** was derivatived into azide product **37** by methanesulfylation with MsCl, and then nucleophilic substitution with NaN_3 [43]. Cyclization of **37** with substituted phenylacetylenes **23** produced triazole product **38** [39], which was followed by reduction with $NaBH_4$ to give alcohol **39** [44]. Finally, deprotection of **39** under the conditions of concentrated hydrochloric acid formed the various substituted aminoalcohols **30a**, **30c**, **30e**, **30g**, **30i** and **30k**. Similarly, their enantiomers **30b**, **30d**, **30f**, **30h**, **30j** and **30l** were prepared from Boc-D-serine methyl ester **40** as a starting material.

3. Results and discussion

3.1. In vitro antibacterial activity of N11-, C12- and C13-substituted homo-aza-clarithromycin derivatives

The *in vitro* antibacterial activity against various sensitive and resistant bacterial strains were reported as minimum inhibitory concentration (MIC) that were determined by the broth microdilution method [45]. The tested sensitive bacterial strains included three different penicillin-susceptible strains (*E. coli* ATCC25922, *P. aeruginosa* ATCC27853 and *B. subtilis* ATCC9372) and one erythromycin-susceptible strain (*S. aureus* ATCC25923). In addition, a variety of resistant bacterial strains were included in the tests in order to identify the potential N11-, C12- and C13-substituted 15-membered homo-aza-



Scheme 2. Regents and conditions: (a) NaN_3, H_2O, 80 °C, 24 h, 88%; (b) **14**, $CuSO_4$, L-ascorbic acid sodium salt, MeOH-H_2O, 40 °C, 24 h, 51–98%; (c) Dess-Martin periodinane, DCM, rt, 1 h, 62–91%.

clarithromycin derivatives that could overcome bacterial resistance. Three different erythromycin-resistant strains (*S. pneumoniae* B1, *S. pneumoniae* AB11 and *S. pyogenes* 1), one penicillin-resistant strain (*S. aureus* ATCC31007) and one methicillin-resistant strain (*S. aureus* ATCC43300) were also tested for the antibacterial activity of compounds. CAM and AZM were used as the reference compounds *in vitro* antibacterial activity assays.

3.1.1. *In vitro antibacterial activity of Series A (**11a**-**11m**)*

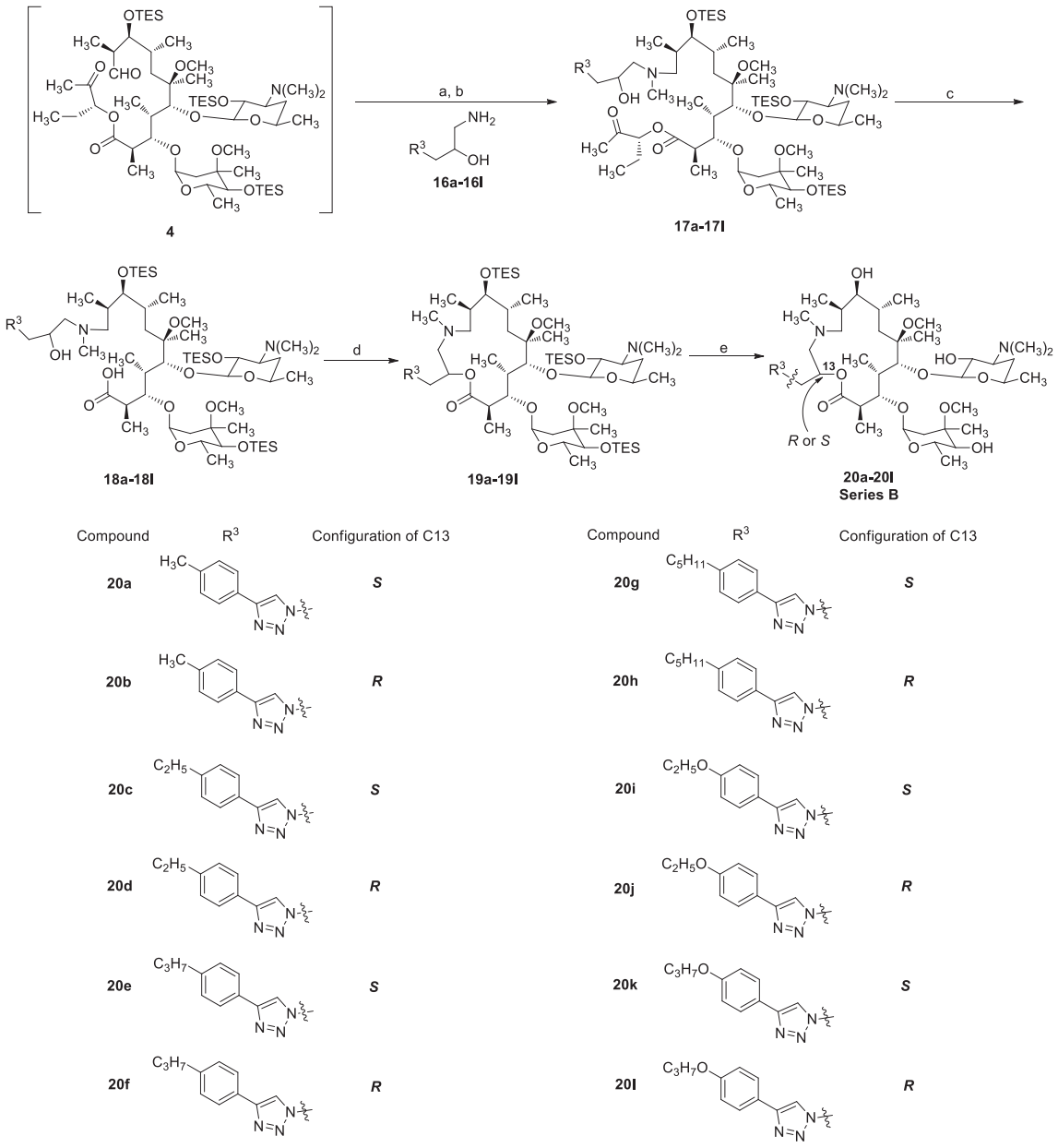
The antibacterial activity of Series A is shown in Table 1. In general, the compounds of Series A were inactive against *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853. In contrast, the compounds of Series A were observed to exhibit excellent antibacterial activity against *S. aureus* ATCC25923 (MIC = 1–8 μg/mL) and *B. subtilis* ATCC9372 (MIC = 1–4 μg/mL). Among them, **11b** showed the most potent activity against *S. aureus* ATCC25923 (MIC = 1 μg/mL) and *B. subtilis* ATCC9372 (MIC = 1 μg/mL). As for activity against the five resistant bacterial strains (*S. aureus* ATCC31007, *S. aureus* ATCC43300, *S. pneumoniae* B1, *S. pneumoniae* AB11 and *S. pyogenes* 1), **11f** and **11g** were found to display a substantial improvement (a 16–64 fold increase) over CAM. Moreover, **11c**, **11d**, **11e**, **11j**, **11k** and **11l** were also more active than CAM against the above five resistant bacterial strains. In particular, **11g** exerted the strongest antibacterial effectiveness against the above five resistant bacterial strains with balanced activity (MIC = 4 ~ 8 μg/mL).

Based on the MIC data mentioned above in our study, and the structure–activity relationships (SARs) of Series A against sensitive bacterial strains are summarized as follows. Introduction of 4-substituted phenyl-1*H*-1,2,3-triazole or 2-pyridine-1*H*-1,2,3-triazole side chain at the N11 position results in a very similar profile in activity against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372. **11a-11c** and **11h-11m** were slightly less active than CAM against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372, but the antibacterial activity of these two kinds of compounds is similar. Actually, introduction of the 4-substituted phenyl-1*H*-1,2,3-triazole side chain at the N11 position may not affect the binding ability of 2′-OH to A2058 and A2059 in domain V of 23S rRNA of bacterial ribosome [33]. In contrast, loss of activity against *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853 was observed for introduction of various 4-substituted phenyl-1*H*-1,2,3-triazole (**11a-11l**) or 2-pyridine-1*H*-1,2,3-triazole (**11m**) at the N11 position. We also observed that their lipid/water partition coefficients (ClogP) values did not affect the anti-sensitive bacteria activity of Series A.

On the other hand, the SARs of Series A against resistant bacteria are also summarized as follows. The substituent on the 4-phenyl-1*H*-1,2,3-triazole and its length is critical to antibacterial activity as shown by **11a-11g** vs **11h-11m**. Introduction of an alkyl chain into the 4-phenyl-1*H*-1,2,3-triazole at the N11 position (**11a-11g**) leads to dramatically increased activity against resistant strains. For example, the ClogP values of **11a-11g** generally increased with the extension of alkyl chain on the 4-phenyl-1*H*-1,2,3-triazole, while their activity against *S. pneumoniae* AB11 was gradually enhanced (**Fig. S1**, see Supplementary Data). Obviously, **11g** possessed the most significant activity against resistant bacteria with a balanced spectrum. Those findings clearly indicate that the alkyl chains with appropriate length and flexibility may easy generate the π-π stacking, electrostatic or hydrophobic interaction with U790 of 23S rRNA [19,32]. We infer that the enhancement of the antibacterial activity achieved by introducing the alkyl group is mainly due to production of a secondary interaction with the binding sites of 23S rRNA. Besides, **11h-11j** had similar trend in antibacterial activity to **11a-11g**. Introduction of halogen group into the 4-phenyl-1*H*-1,2,3-triazole (**11k** and **11l**) results in very potent activity against resistant bacteria (MIC ranges from 16 to 128 μg/mL). It may be because that introduction of halogen group can improve the liposolubility of compounds, which may explain why **11k** and **11l** have the desired profile of antibacterial activity.

3.1.2. *In vitro antibacterial activity of Series B (**20a**-**20l**)*

The antibacterial activity of Series B is shown in Table 2. Most compounds in series B were very effective against *S. aureus* ATCC25923 (MIC = 0.5–2 μg/mL) and *B. subtilis* ATCC9372 (MIC = 0.25–1 μg/mL). Among them, **20c**, **20d** and **20f** exhibited not only the most potent activity against *S. aureus* ATCC25923 (MIC = 0.5, 0.5 and 0.5 μg/mL), but also the strongest activity against *B. subtilis* ATCC9372 (MIC ≤ 0.25, 0.25 and 0.25 μg/mL). Interestingly, all compounds of Series B possessed improved activity against the five resistant bacterial strains of *S. aureus* ATCC31007, *S. aureus* ATCC43300, *S. pneumoniae* B1, *S. pneumoniae* AB11 and *S. pyogenes* 1 compared with CAM and AZM. In particular, **20g**

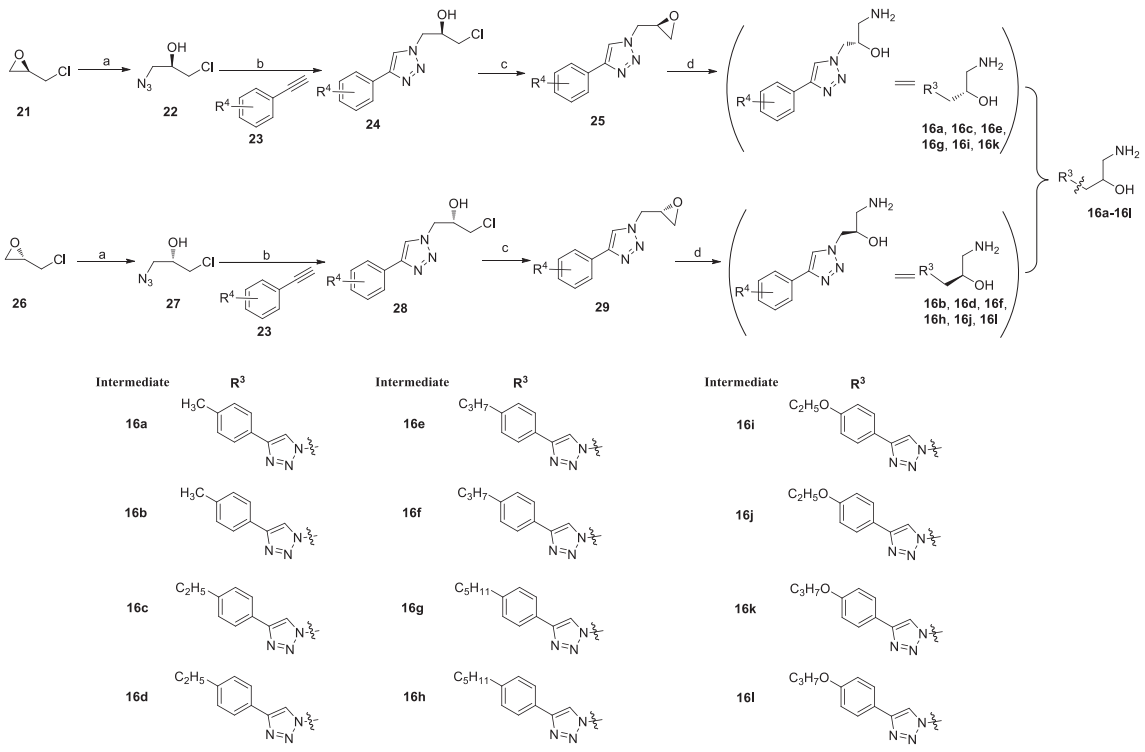


Scheme 3. Regents and conditions: (a) **16a-16l**, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (b) HCHO, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (c) LiOH, THF-C_2H_5OH-H_2O, rt, 6 h, 27–88% in four steps from **3**; (d) i) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, THF, rt, 4 h; ii) DMAP, CH_3CN, reflux, 0.5 h, 41–89%; (e) Hydrogen fluoride-pyridine (65% in hydrofluoric acid), THF, rt, 18 h, 24–63%.

and **20h** showed the most greatly improved activity (4–8 μg/mL) against the above five resistant bacterial strains, which was 16–32-fold stronger than those of CAM and AZM, while **20c**, **20e**, **20f** and **20l** exhibited moderately enhanced activity as compared to CAM. However, all compounds of Series B completely abolished the activity against *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853.

The SARs of Series B against sensitive bacterial strains have been systematically summarized as follows. Introduction of the 4-substituted phenyl-1*H*-1,2,3-triazole side chain at the C13 position can significantly improve antibacterial activity against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372, which was illustrated by the examples of **20a**-**20h** with the MIC values of 1–8 μg/mL. In a remarkable contrast, this modification is not necessary for activity against *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853, which was confirmed by the fact that the MIC values of **20a**-**20l** are more than 32 μg/mL. The more important concern is that C13 is chirality, which results in the compounds of Series B with *R*- and *S*-configurations. *R*-isomer, in general, exhibited 8- to 64-fold better activity than *S*- isomer against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372 (The order of activity: **20f** > **20e**, **20h** > **20g**, **20j** > **20i** and **20l** > **20k**). Thus, the *R*-configuration of C13 has favorable effects on antibacterial activity.

On the other hand, introduction of an alkyl group into the 4-phenyl-1*H*-1,2,3-triazole at the C13 position greatly increased activity against resistant strains (**20a**, **20c**, **20e** and **20g**). Moreover, we also observed that the longer the alkyl group was, the higher the ClogP value was, and the stronger its antibacterial activity was. For instance, **20g** with *n*-amyl group had the most potent activity against *S. pneumoniae* AB11 (The order of activity: **20g** > **20e** > **20c** > **20a**) (**Fig. S2**, see Supplementary Data). The above findings may indicate that the length and flexibility of the alkyl group has a dramatic effect on the binding force of compounds (**20a**, **20c**, **20e** and **20g**) for new binding site U790 [19,32]. Similarly, the same trend was also observed for **20b**, **20d**, **20f** and **20h** (**Fig. S3**, see Supplementary Data). Besides, the activity of the compounds with *R*-configuration at the C13 position was essentially equivalent to that of



Scheme 4. Regents and conditions: (a) NaN_3, AcOH-H_2O, 30 °C, 5 h, 86–90%; (b) **23**, $CuSO_4$, L-ascorbic acid sodium salt, CH_3OH-H_2O, 35–40 °C, 24 h, 62–97%; (c) NaOH, CH_3CN-H_2O, rt, 2 h; (d) 25% NH_3·H_2O, CH_3CN, rt, 3 h, 41–76% in two steps from **24** or **28**.

the compounds with *S*-configuration against resistant bacteria (The order of activity: **20a** = **20b**, **20c** ≈ **20d**, **20e** ≈ **20f**, **20g** ≈ **20h**, **20i** = **20j** and **20k** ≈ **20l**), which reveals that the chirality of C13 has no influence on activity against resistant bacteria.

3.1.3. *In vitro antibacterial activity of Series C (34a-34l)*

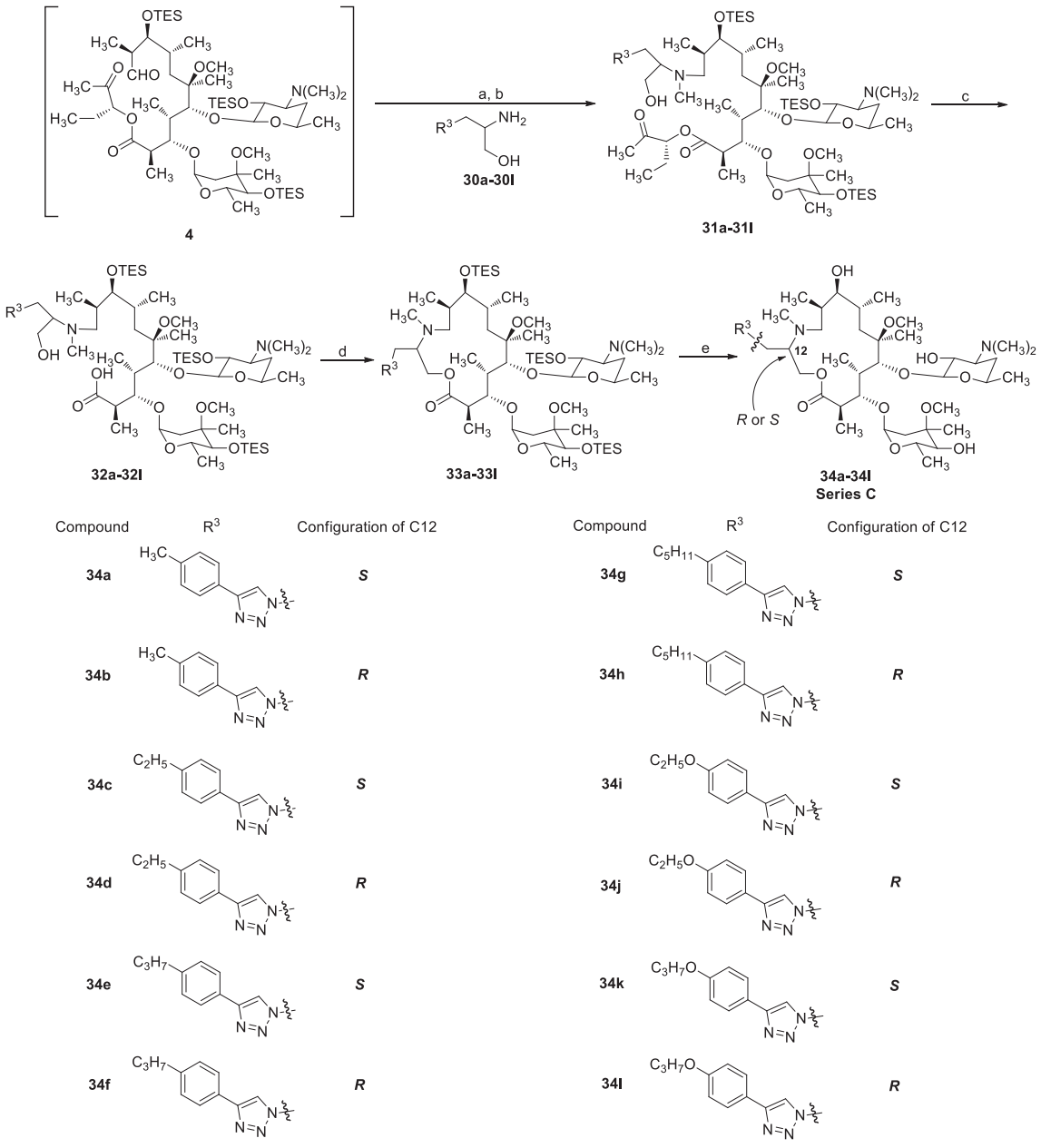
The antibacterial activity of Series C is shown in Table 3. In this series, **34h**, **34i** and **34k** were found to possess potent activity against *B. subtilis* ATCC9372 with the MIC values of 1, 1 and 0.5 μg/mL, respectively, which were fundamentally equivalent to that CAM. They also showed activity against *S. aureus* ATCC25923 with the MIC values of 4, 2 and 1 μg/mL, respectively, but were slightly less active than CAM. Especially, **34k** exhibited the most potent and balanced activity against both *S. aureus* ATCC25923 and *B. subtilis* ATCC9372. **34g** and **34h** had excellent activity against the five resistant bacterial strains of *S. aureus* ATCC31007, *S. aureus* ATCC43300, *S. pneumoniae* B1, *S. pneumoniae* AB11 and *S. pyogenes* 1, which were 16- to 64-fold more active than those of CAM. In addition, **34c**, **34d**, **34e** and **34k** had a moderate activity against the above resistant bacterial strains, which were generally 4- to 16-fold better than those of CAM. Among them, **34g** exhibited the most potent and balanced activity against with the MIC values of 4–8 μg/mL. However, the compounds of Series C (**34a-34l**) exhibited poor activity against *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853.

According to the data of antibacterial activity, the SARs of Series C against sensitive strains were summarized in detail. Introduction of a 4-substituted phenyl-1*H*-1,2,3-triazole side chain at the C12 position fails to improve activity against *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853. In contrast, moderate improvements in activity against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372 were observed for introduction of the above side chain. Similar to Series B, introduction of a 4-substituted phenyl-1*H*-1,2,3-triazole side chain at the C12 position leads to the chirality of C12, thereby producing the compounds with *R*- and *S*-configurations. As for their antibacterial activity, the compounds with *S*-configuration was in general 8- to 64-fold better than the compounds with *R*-configuration against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372 (The order of activity: **34e** > **34f**, **34i** > **34j** and **34k** > **34l**).

On the other hand, comparison of the activity of **34a**, **34c**, **34e** and **34g** against resistant bacteria with the reference CAM reveals that the order of activity of the above compounds against *S. pneumoniae* AB11 is the **34g** > **34e** ≈ **34c** > **34a**, which displays that the length of the introduced alkyl group is beneficial to the activity against *S. pneumoniae* AB11 (**Fig. S4**, see Supplementary Data). That may be because the suitable length and flexibility of the alkyl group are good for tightly interacting with the new binding site U790 [19,32]. Besides, **34b**, **34d**, **34f** and **34h** possess the similar trend in antibacterial activity to **34a**, **34c**, **34e** and **34g** (**Fig. S5**, see Supplementary Data). The relationships between ClogP values and the activity of **34a-34h** against resistant bacteria revealed that the higher values of ClogP (>6) of compound led to its better antibacterial activity. It is worth noting that isomers **34a** and **34b** exhibited same activity against resistant bacteria, which indicates that the configuration of C12 position is does not affect the antibacterial activity. Similarly, the conclusion also applies to **34c** and **34d**, **34e** and **34f**, **34g** and **34h**. However, the antibacterial activity of compounds with alkoxy group is not different from that of the above compounds. For example, **34i** with alkoxy group displayed a 2–4-fold improvement in antibacterial activity as compared to its epimer **34j** against resistant bacteria, and **34k** with alkoxy group exhibited increased antibacterial activity as compared to its epimer **34l** as well.

3.1.4. *Overall SARs of Series A, B and C*

Overall, in the antibacterial activity against susceptible bacteria, the activity of these three series is B > A > C. This indicates that antibacterial activity depends on the position of the 4-substituted phenyl-1*H*-1,2,3-triazole side chain attached to the macrolide skeleton. For example, introduction of the 4-substituted phenyl-1*H*-1,2,3-triazole side chain at the C13 position had the greatest effect on the antibacterial activity, followed by that at the N11 position and the worst at the C12 position. The above findings may show that introduction of the appropriate side chains at the C13 position has little effect on the binding of 2′-OH to A2058 and A2059 in domain V of 23S rRNA [33]. On the other

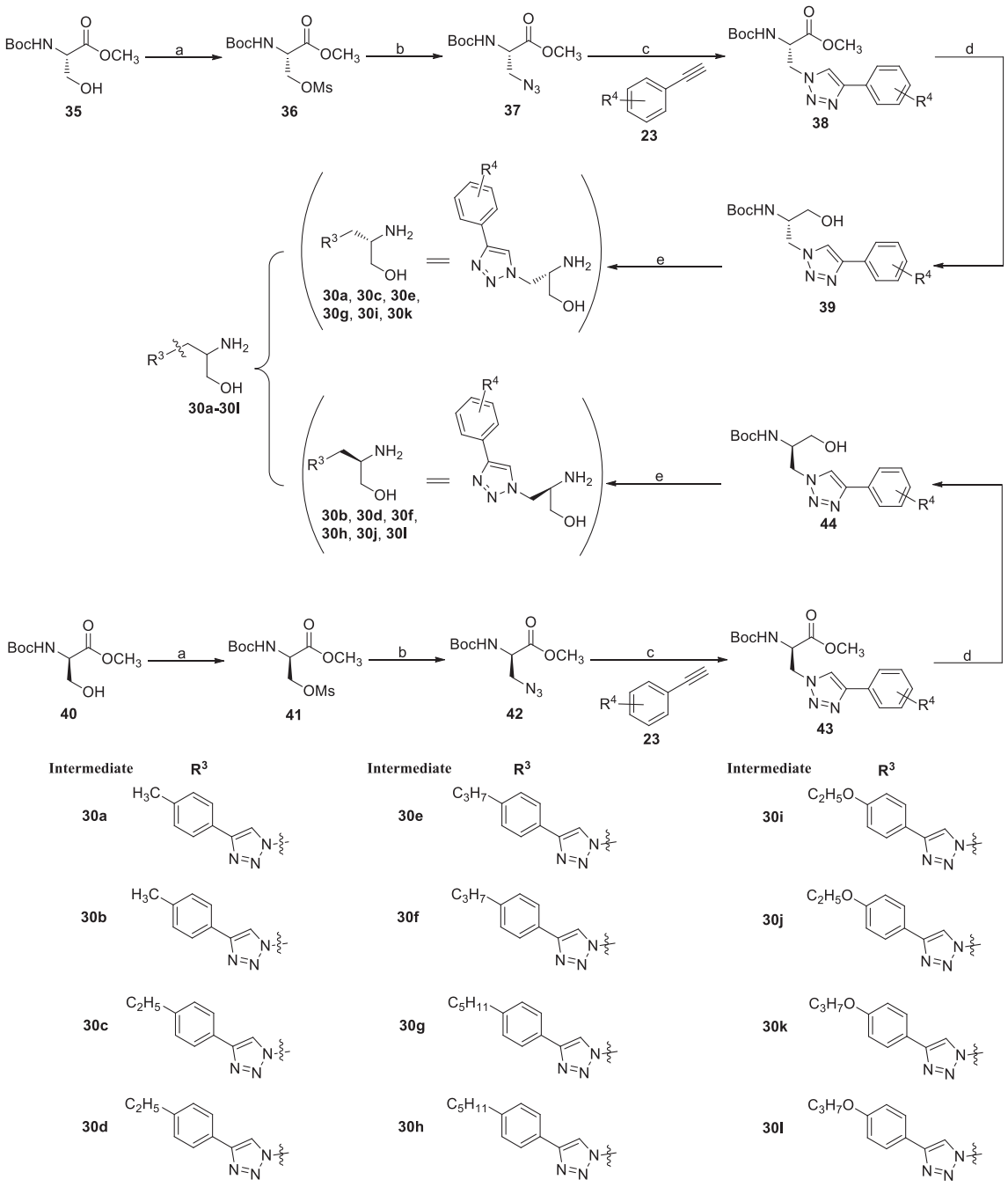


Scheme 5. Regents and conditions: (a) **30a-30l**, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (b) HCHO, $NaBH(OAc)_3$, $CHCl_3$, rt, 4 h; (c) LiOH, THF-C_2H_5OH-H_2O, rt, 6 h, 15–77% in four steps from **3**; (d) i) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, THF, rt, 4 h; ii) DMAP, CH_3CN, reflux, 0.5 h, 22–81%; (e) Hydrogen fluoride-pyridine (65% in hydrofluoric acid), THF, rt, 18 h, 24–83%.

hand, Series A, B and C displayed similar activity against resistant bacteria, which reveals that the introduction position of the 4-substituted phenyl-1*H*-1,2,3-triazole side chain is not related to the antibacterial activity. It is worth noting that introduction of 4-*n*-amylphenyl-1*H*-1,2,3-triazole side chain could lead to the strongest activity against resistant bacteria with a balanced spectrum (**11g**, **20g**, **20h**, **34g** and **34h**). This may be due to *n*-amyl group with the most suitable length and flexibility for interaction with U790 [19,32]. Besides, it also might be explained by the possibility that higher lipophilic compounds were easily transported to the binding sites of microorganism. Therefore, we can draw the important conclusions as follows: (1) When introduction of an alkyl group into phenyl-1*H*-1,2,3-triazole side chain at the N11, C12 or C13 position, the longer the alkyl chain is (5 carbon is the best), the stronger the activity against resistant bacteria is; (2) The compounds containing alkyl groups are more active against resistant bacteria than the compounds containing alkoxy groups; (3) The introduction of 4-substituted phenyl-1*H*-1,2,3-triazole side chain at the N11, C12 and C13 position of 15-membered skeleton can effectively enhance the activity against resistant bacteria.

3.2. Molecular docking

In order to investigate the potential binding mode of compounds, **11g** and **20c** were selected as representative compounds for molecular docking because they were the most potent compounds against drug-resistant and susceptible bacteria. Here, the computational analyses of **11g**, **20c** and CAM were explored utilizing a reported crystal structure of *E. coli* ribosome bound to antibiotics (PDB code: 4V7S [31]) and autodock. The molecular docking of **11g** and CAM is shown in Fig. 6. We observed that the macrolide skeleton of **11g** and CAM are basically in the same space (Fig. 6**a**), while the 4-*n*-amylphenyl-1*H*-1,2,3-triazole side chain of **11g** extends to the vicinity of U790 (Fig. 6**b**). This indicates



Scheme 6. Regents and conditions: (a) MsCl, DCM, Et_3N, 0 °C, 0.5 h; (b) NaN_3, DMF, 50 °C, 0.5 h; (c) **23**, $CuSO_4$, L-ascorbic acid sodium salt, CH_3OH-H_2O, 35–40 °C, 48 h, 36–62%; (d) $NaBH_4$, CH_3OH, 0 °C, 2 h; (e) aq HCl, EtOAc, rt, 4 h, 40–85% in two steps from **38** or **43**.

that the side chain may bind to U790 by π-π stacking, electrostatic or hydrophobic interaction. We also observed that the aralkyl side chains of **11g** and telithromycin had the same spatial extension direction, which implied that theypossessed the same binding sites (Fig. 6**c**). In the same way, the model of **20c** and CAM docked into *E. coli* ribosome (PDB code: 4V7S [31]) was presented in Fig. 7. The results indicate that the stereo conformation of 15-membered homo-aza-clarithromycin skeleton of **20c** and the macrocyclic lactone of CAM are located in approximately the same spatial area in *E. coli* ribosome (Fig. 7**a**). In addition, the strong hydrogen bond interaction of the 2′-OH of **20c** with A2058 and A2059 was also observed (Fig. 7**b**). This may be helpful to explain why **20c** has excellent activity against susceptible bacteria.

3.3. Bactericidal or bacteriostatic effect

The minimal bactericidal concentration (MBC) values of some promising compounds against susceptible bacteria (*S. aureus* ATCC25923) and resistant bacteria (*S. pneumoniae* AB11) was determined to confirm whether those promising compounds were bactericidal or bacteriostatic (Table 4). The results showed that **20c**, **20d** and **20f** possessed the MBC/MIC values of 64–128, which suggests that they are bacteriostatic agents with regard to *S. aureus* ATCC25923. In contrast, the MBC/MIC values of 16 were observed for **11f**, **11g**, **20g**, **20h** and **34g**, which indicates that they exhibit bacteriostatic effect against *S. pneumoniae* AB11. In short, the above compounds exhibit potent activity against *S. aureus* ATCC25923 and *S. pneumoniae* AB11 by bacteriostatic mechanism.

Table 1
In vitro antibacterial activity and ClogP of Series A (**11a-11m**).

Compound	Minimum inhibitory concentration / MIC (μg/mL)									ClogP[j]
	S. aureus ATCC25923[a]	*E. coli* ATCC25922[b]	*P. aeruginosa* ATCC27853[c]	*B. subtilis* ATCC9372[d]	*S. aureus* ATCC31007[e]	*S. aureus* ATCC43300[f]	*S. pneumoniae* B1[g]	*S. pneumoniae* AB11[h]	*S. pyogenes* 1[i]	
11a	2	>128	128	1	256	256	64	128	64	3.79
11b	1	>128	128	1	64	64	32	128	32	4.28
11c	2	>128	128	1	32	32	16	32	16	4.94
11d	4	>128	128	2	16	16	8	32	16	5.47
11e	8	>128	128	2	16	8	16	16	8	5.61
11f	8	>128	128	2	8	8	8	8	8	6.00
11g	8	>128	128	4	4	4	8	4	8	6.53
11h	2	>128	128	1	256	128	64	256	64	3.90
11i	2	>128	128	2	128	64	32	128	32	4.43
11j	2	>128	128	2	32	32	32	32	16	4.96
11k	2	>128	128	1	64	64	32	128	32	3.97
11l	2	>128	128	1	32	32	16	32	16	4.54
11m	2	>128	128	1	>256	>256	256	128	64	2.67
AZM	≤0.25	64	16	≤0.25	>256	>256	>256	256	256	2.64
CAM	≤0.25	128	32	≤0.25	>256	>256	>256	128	256	2.37

[a] *S. aureus* ATCC25923: *Staphylococcus aureus* ATCC25923, erythromycin-susceptible strain;
[b] *E. coli* ATCC25922: *Escherichia coli* ATCC25922, penicillin-susceptible strain;
[c] *P. aeruginosa* ATCC27853: *Pseudomonas aeruginosa* ATCC27853, penicillin-susceptible strain, not characterized;
[d] *B. subtilis* ATCC9372: *Bacillus subtilis* ATCC9372, penicillin-susceptible strain;
[e] *S. aureus* ATCC31007: *Staphylococcus aureus* ATCC31007, penicillin-resistant strain;
[f] *S. aureus* ATCC43300: *Staphylococcus aureus* ATCC43300, methicillin-resistant strain;
[g] *S. pneumoniae* B1: *Streptococcus pneumoniae* B1, erythromycin-resistant strain expressing the *erm*B gene;
[h] *S. pneumoniae* AB11: *Streptococcus pneumoniae* AB11, erythromycin-resistant strain expressing the *erm*B and *mef*A genes;
[i] *S. pyogenes* 1: *Streptococcus pyogenes* 1, erythromycin-resistant strain isolated clinically;
[j] ClogP: The theoretically calculated values of ClogP for all the target compounds were calculated using SYBYL-X 2.1.1.

Table 2
In vitro antibacterial activity and ClogP of Series B (**20a-20 l**).

Compound	Minimum inhibitory concentration / MIC (μg/mL)									ClogP[j]
	S. aureus ATCC25923[a]	*E. coli* ATCC25922[b]	*P. aeruginosa* ATCC27853[c]	*B. subtilis* ATCC9372[d]	*S. aureus* ATCC31007[e]	*S. aureus* ATCC43300[f]	*S. pneumoniae* B1[g]	*S. pneumoniae* AB11[h]	*S. pyogenes* 1[i]	
20a	2	64	128	1	64	64	64	64	64	3.97
20b	1	32	64	1	64	64	64	64	64	3.97
20c	0.5	128	128	≤0.25	32	32	32	32	32	4.50
20d	0.5	32	64	≤0.25	128	64	64	64	64	4.50
20e	8	>128	128	2	16	8	16	16	16	5.03
20f	0.5	32	64	≤0.25	32	32	32	32	16	5.03
20g	8	>128	128	8	8	8	8	4	8	6.09
20h	1	>128	>128	1	8	8	8	8	8	6.09
20i	32	>128	128	64	64	64	64	64	64	3.99
20j	2	64	64	1	64	64	64	64	64	3.99
20k	16	>128	128	4	64	32	64	32	32	4.52
20l	1	64	64	0.5	32	32	64	32	32	4.52
AZM	≤0.25	64	16	≤0.25	>256	>256	>256	256	256	2.64
CAM	≤0.25	128	32	≤0.25	>256	>256	>256	128	256	2.37

[a] *S. aureus* ATCC25923: *Staphylococcus aureus* ATCC25923, erythromycin-susceptible strain;
[b] *E. coli* ATCC25922: *Escherichia coli* ATCC25922, penicillin-susceptible strain;
[c] *P. aeruginosa* ATCC27853: *Pseudomonas aeruginosa* ATCC27853, penicillin-susceptible strain, not characterized;
[d] *B. subtilis* ATCC9372: *Bacillus subtilis* ATCC9372, penicillin-susceptible strain;
[e] *S. aureus* ATCC31007: *Staphylococcus aureus* ATCC31007, penicillin-resistant strain;
[f] *S. aureus* ATCC43300: *Staphylococcus aureus* ATCC43300, methicillin-resistant strain;
[g] *S. pneumoniae* B1: *Streptococcus pneumoniae* B1, erythromycin-resistant strain expressing the *erm*B gene;
[h] *S. pneumoniae* AB11: *Streptococcus pneumoniae* AB11, erythromycin-resistant strain expressing the *erm*B and *mef*A genes;
[i] *S. pyogenes* 1: *Streptococcus pyogenes* 1, erythromycin-resistant strain isolated clinically;
[j] ClogP: The theoretically calculated values of ClogP for all the target compounds were calculated using SYBYL-X 2.1.1.

3.4. Study on bactericidal kinetics

Based on the above mentioned MBC/MIC data, **11g** was found to have a certain degree of bactericidal activity. Next, we investigated how rapidly **11g** were able to reduce a high amount of *S. pneumoniae* AB11 using a time-bactericidal assay (Fig. 8). The results displayed that at the concentrations of 1, 2 and 4 MIC, this compound exhibited bactericidal activity as it produced a 2.7 $\log_{10}$, 3.14 $\log_{10}$ and 3.31 $\log_{10}$ reduction in *S. pneumoniae* AB11 CFU/mL (0–12 h), respectively. In contrary, this compound showed excellent bacteriostatic activity as it did not produce a significant $\log_{10}$ reduction in *S. pneumoniae* AB11 CFU/mL (12–24 h). Thus, **11g** have a bacteriostatic effect on bacterial proliferation, which is dependent on its concentration and timing.

Table 3
In vitro antibacterial activity and ClogP of Series C (**34a-34 l**).

Compound	Minimum inhibitory concentration / MIC (μg/mL)									ClogP[j]
	S. aureus ATCC25923[a]	*E. coli* ATCC25922[b]	*P. aeruginosa* ATCC27853[c]	*B. subtilis* ATCC9372[d]	*S. aureus* ATCC31007[e]	*S. aureus* ATCC43300[f]	*S. pneumoniae* B1[g]	*S. pneumoniae* AB11[h]	*S. pyogenes* 1[i]	
34a	16	>128	128	8	128	128	128	64	64	3.97
34b	16	>128	128	16	128	128	128	128	64	3.97
34c	16	>128	128	8	32	32	32	32	16	4.50
34d	32	>128	128	8	32	32	32	32	16	4.50
34e	8	>128	128	4	16	32	32	32	32	5.03
34f	64	>128	128	32	128	64	64	32	16	5.03
34g	8	>128	128	4	8	4	8	8	8	6.09
34h	4	>128	128	1	8	8	8	8	8	6.09
34i	2	>128	128	1	64	64	64	64	64	3.99
34j	64	>128	128	32	256	256	256	128	128	3.99
34k	1	128	64	0.5	32	32	32	32	32	4.51
34l	64	>128	128	16	128	128	128	128	32	4.51
AZM	≤0.25	64	16	≤0.25	>256	>256	>256	256	256	2.64
CAM	≤0.25	128	32	≤0.25	>256	>256	>256	128	256	2.37

[a] *S. aureus* ATCC25923: *Staphylococcus aureus* ATCC25923, erythromycin-susceptible strain;
[b] *E. coli* ATCC25922: *Escherichia coli* ATCC25922, penicillin-susceptible strain;
[c] *P. aeruginosa* ATCC27853: *Pseudomonas aeruginosa* ATCC27853, penicillin-susceptible strain, not characterized;
[d] *B. subtilis* ATCC9372: *Bacillus subtilis* ATCC9372, penicillin-susceptible strain;
[e] *S. aureus* ATCC31007: *Staphylococcus aureus* ATCC31007, penicillin-resistant strain;
[f] *S. aureus* ATCC43300: *Staphylococcus aureus* ATCC43300, methicillin-resistant strain;
[g] *S. pneumoniae* B1: *Streptococcus pneumoniae* B1, erythromycin-resistant strain expressing the *erm*B gene;
[h] *S. pneumoniae* AB11: *Streptococcus pneumoniae* AB11, erythromycin-resistant strain expressing the *erm*B and *mef*A genes;
[i] *S. pyogenes* 1: *Streptococcus pyogenes* 1, erythromycin-resistant strain isolated clinically;
[j] ClogP: The theoretically calculated values of ClogP for all the target compounds were calculated using SYBYL-X 2.1.1.

3.5. Cytotoxic assay

In the three series, **20c**, **20d** and **20f** were selected for cytotoxic assay due to their potent activity against *S. aureus* ATCC25923 and *B. subtilis* ATCC9372 with the MIC values in the low concentration range (0.25–0.5 μg/mL), which is equivalent to that of CAM. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method was used to evaluate the cytotoxicity of those compounds to MCF-7 breast cancer cells (Fig. 9). The result represented that **20c** and **20f** were non-toxic to MCF-7 breast cancer cells at the concentration of 8 μg/mL, because their cell survival rate was still more than 50% at this concentration, and **20d** was non-toxic to MCF-7 breast cancer cells at the concentration of 16 μg/mL. Therefore, **20c**, **20d** and **20f** exhibit no cytotoxicity at its effective antibacterial concentration.

4. Conclusion

Novel N11-, C12- and C13-substituted 15-membered homo-aza-clarithromycin derivatives against various sensitive and resistant bacteria were designed, synthesized and evaluated for their antibacterial activity. The C13-substituted derivatives **20c**, **20d** and **20f** possessed both the most potent activity against *S. aureus* ATCC25923 with the MIC values of 0.5, 0.5 and 0.5 μg/mL, and *B. subtilis* ATCC9372 with the MIC values of less than or equal to 0.25, 0.25 and 0.25 μg/mL, respectively. In particular, the N11-substituted derivative **11g** exhibited the strongest activity against all the tested resistant bacterial strains with the MIC values of 4–8 μg/mL, and exerted a bacteriostatic effect on bacterial proliferation. This may be because it produced an additional binding force with U790 in addition to the normal binding force of macrolide skeleton. Moreover, **20c**, **20d** and **20f** were non-toxic to human breast cancer MCF-7 cells at its effective antibacterial concentration. Taken all together, **20c**, **20d**, **20f** and **11g** become visible as forward-looking and promising lead compounds for further investigation.

5. Experimental section

5.1. Synthetic procedures

The structures were identified by spectral analysis. ^{1}H NMR and ^{13}C NMR spectra were all given on Bruker Avance DRX600 spectrometer (600 MHz for ^{1}H NMR, 100 or 150 MHz for ^{13}C NMR) and measured in $CDCl_3$ or d_6-DMSO. Mass spectra and high resolution mass spectra were recorded on the API 4000 instrument and Orbitrap analyzer, respectively. The melting points of compounds were determined on an uncorrected RY-1 melting point apparatus. All reagents and solvents were used directly without prior separation and purification, except where noted. The chemical synthesis reaction was monitored by thin layer chromatography. Isolation and purification of intermediates and target compounds were carried out on the column chromatography of silica gel.

5.1.1. Synthesis of N11-substituted 15-membered homo-aza-clarithromycin derivatives (Series A)

*5.1.1.1. 3-Azidopropan-1-ol (**13**).* 3-Bromo-1-propanol **12** (1 g, 7.25 mmol) in H_2O (10 mL) was reacted with NaN_3 (0.94 g, 14.5 mmol) at 80 °C for 24 h. DCM (20 mL) was added, the organic phase was separated and aqueous layer was thoroughly extracted with DCM (20 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo* to yield 3-azidopropan-1-ol **13** (0.64 g, 88%) as a colorless oil.

*5.1.1.1. 3-(4-Phenyl-1H-1,2,3-triazol-1-yl)propan-1-ol (**15**).* **13** (0.5 g, 4.95 mmol) in 75% methanol solution (20 mL) was reacted with phenylacetylene **14** (0.5 g, 4.95 mmol) in the presence of $CuSO_4$ (49 mg) and L-ascorbic acid sodium salt (147 mg) at 40 °C for 24 h. The reaction mixture was evaporated *in vacuo* and the residue was separated chromatographically (DCM/CH_3OH = 30:1) to provide the alcohol **15** (0.8 g, 80%) as a white solid. Mp: 85–88 °C, TLC R_f = 0.47 (DCM/CH_3OH = 20:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84–7.81 (m, 3H), 7.43 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 4.58 (t, J = 6.7 Hz, 2H), 3.70 (t, J = 5.8 Hz, 2H), 2.21–2.17 (m, 2H), 1.72 (s, 1H); MS (ESI) *m/z* calcd for $C_{11}H_{14}N_3O$ $[M + H]^+$: 204.1, found: 204.2.

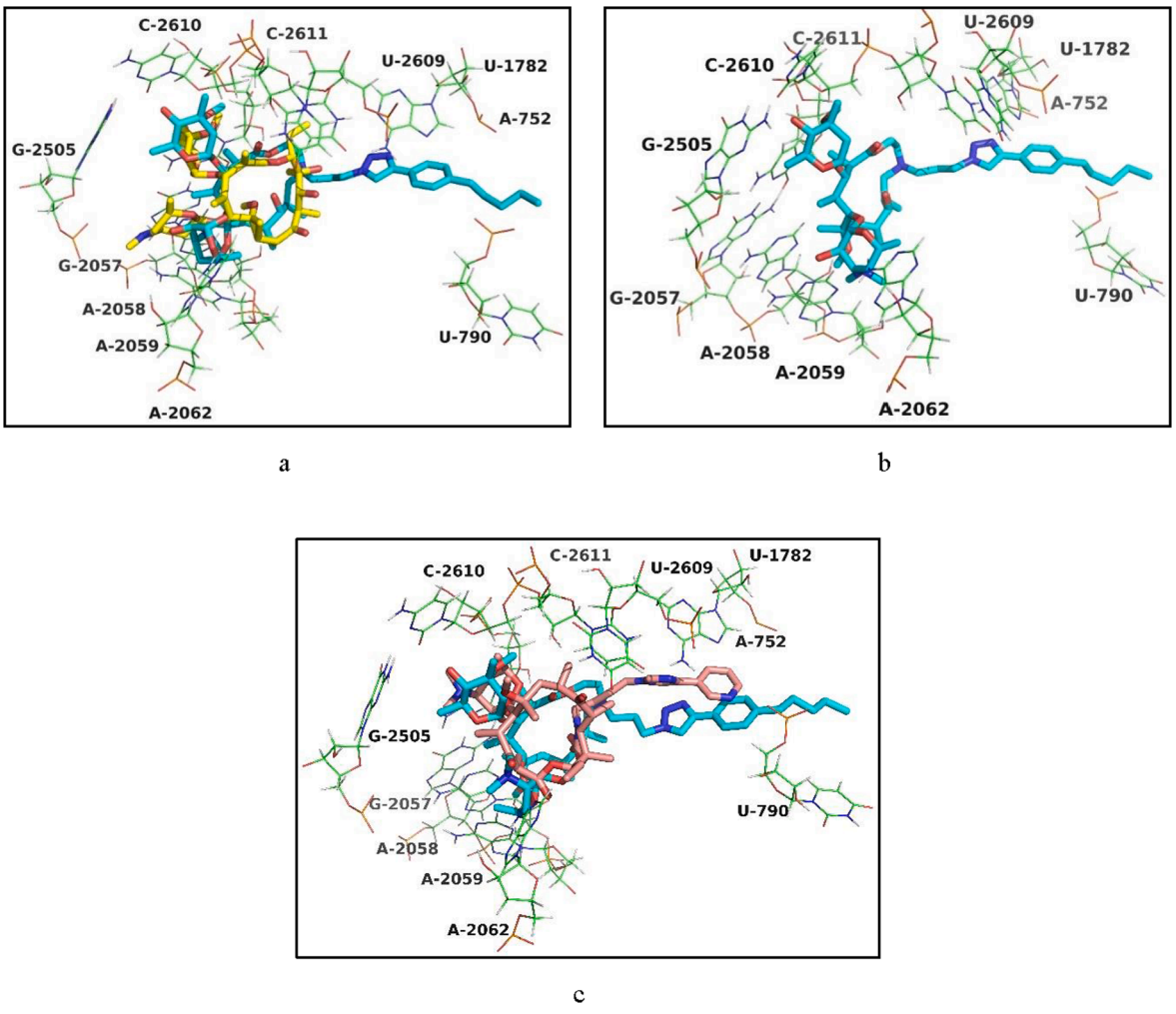


Fig. 6. (**a**) Model of compound **11 g** (wathet) and CAM (yellow) docked into *E. coli* ribosome (PDB code: 4V7S [31]). Both are located in approximately the same spatial area in *E. coli* ribosome; (**b**) The docking model of compound **11g** (wathet) in *E. coli* ribosome; (**c**) Model of compound **11g** (wathet) and telithromycin (reddish brown) docked into *E. coli* ribosome. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

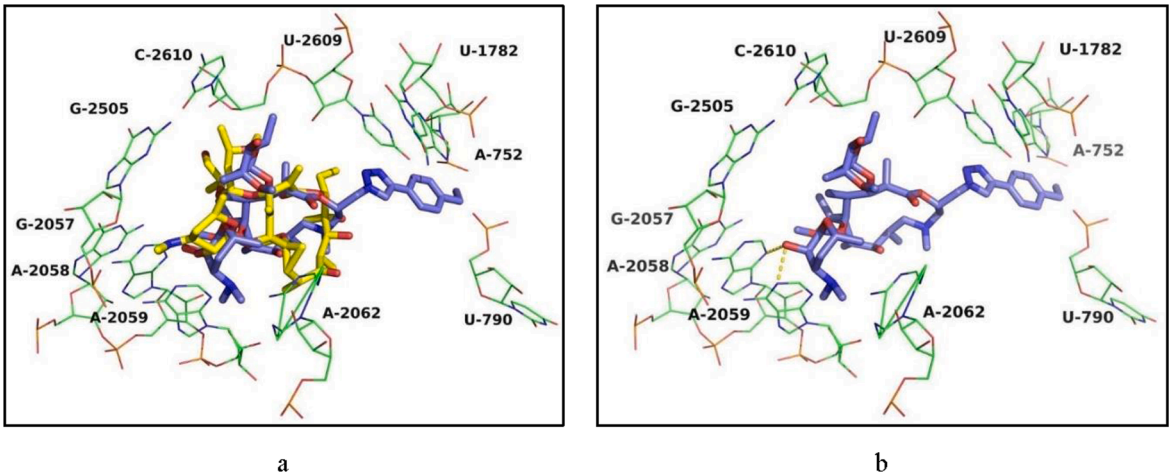


Fig. 7. (**a**) Model of compound **20c** (navy blue) and CAM (yellow) docked into *E. coli* ribosome; (**b**) The docking model of compound **20c** (navy blue) in *E. coli* ribosome. In the model, the predicted hydrogen bonds between compound **20c** and the nucleotide residues are indicated by dotted lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Comparison of MIC and MBC values for some promising compounds against *S. aureus* ATCC25923 and *S. pneumoniae* AB11.

Compound	MBC (μg/mL)	MIC (μg/mL)	MBC/MIC
		S. aureus ATCC25923[a]	
20c	64	0.5	128
20d	32	0.5	64
20f	64	0.5	128
CAM	128	≤0.25	≥512
		S. pneumoniae AB11[b]	
11f	128	8	16
11g	64	4	16
20g	64	4	16
20h	128	8	16
34g	128	8	16
34h	>128	8	>16
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 gene.

*5.1.1.2. 3-(4-Phenyl-1H-1,2,3-triazol-1-yl)propanal (**7a**).* To a solution of **15** (0.5 g, 2.46 mmol) in anhydrous DCM (20 mL) was added Dess-Martin periodinane (1.15 g, 2.71 mmol) at room temperature. After stirring the reaction mixture for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (DCM/CH_3OH = 30:1) to obtain the aldehyde **7a** (0.45 g, 91%) as a light yellow oil.

*5.1.1.3. 9-Dihydro-6-O-methylerythromycin A (**2**).* To a solution of CAM **1** (20 g, 26.8 mmol) dissolved in anhydrous THF (150 mL) and CH_3OH (300 mL) was added $NaBH_4$ (6 g, 158.6 mmol) in three batches within 1 h at 0 °C. The reaction mixture was stirred at room temperature for 24 h under nitrogen atmosphere. The reaction mixture was concentrated *in vacuo* to dryness, and then added DCM (200 mL) and saturated NH_4Cl solution (200 mL). The organic phase was separated and aqueous layer was extracted with DCM (100 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*, and the residue was separated chromatographically (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 30:1:0.1 ~ 20:1:0.1 ~ 10:1:0.1) to form the 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); ^1H NMR (600 MHz, $CDCl_3$, δ ppm): 5.72 (d, *J* = 9.8 Hz, 1H), 5.30 (s, 1H), 5.21 (dd, *J* = 11.2, 2.2 Hz, 1H), 4.96 (dd, *J* = 20.3, 4.7 Hz, 1H), 4.50 (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), 0.84 (t, *J* = 7.4 Hz, 3H); MS (ESI) *m/z* calcd for $C_{38}H_{72}NO_{13}$ $[M + H]^+$: 750.5, found: 750.8.

*5.1.1.4. 2′, 4′′, 9(S)-Triethylsilane-6-O-methylerythromycin A (**3**).* To a solution of **2** (8 g, 10.7 mmol) and imidazole (7.2 g, 105.8 mmol) in anhydrous DMF (100 mL) was added dropwise TESCl (5.5 g, 36.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h under nitrogen atmosphere. The reaction mixture was quenched by addition of H_2O (100 mL), then EtOAc (100 mL) and *n*-hexane (100 mL) were added to this mixture. The organic layer was separated and washed with saturated NH_4Cl solution (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*, and the residue was separated chromatographically (PE/acetone =

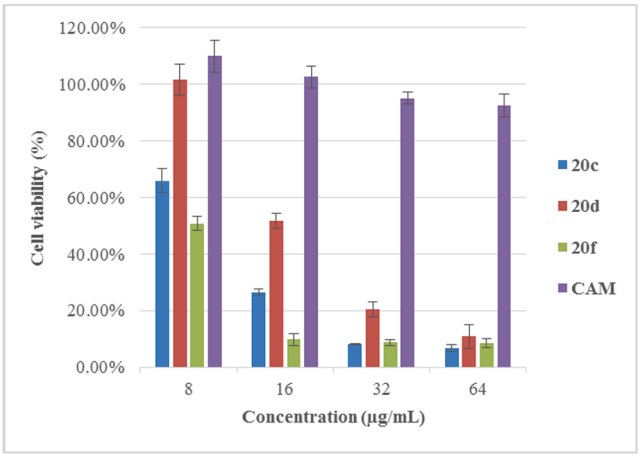


Fig. 9. The toxicity assay of compounds **20c**, **20d** and **20f** to MCF-7 breast cancer cells, and CAM served as a control.

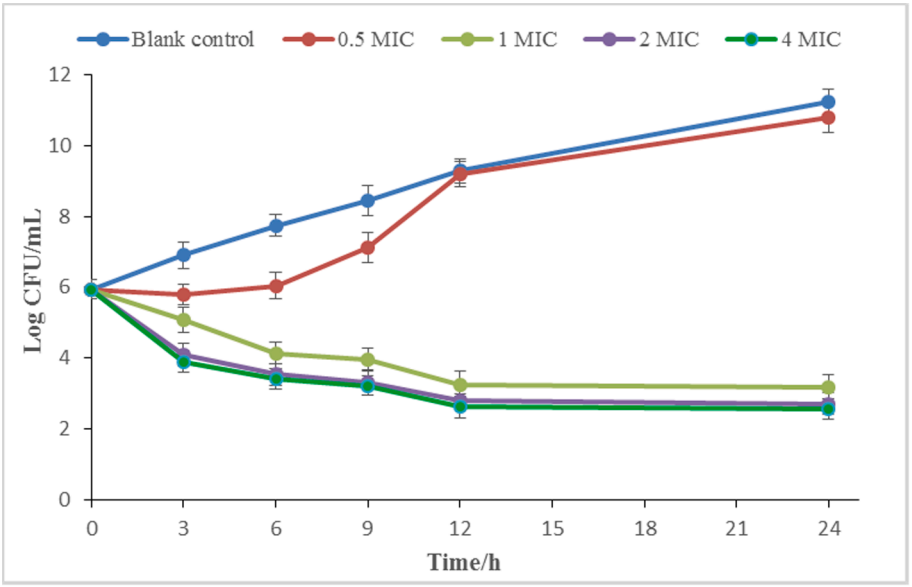


Fig. 8. Bactericidal kinetics of compound **11g** against *S. pneumoniae* AB11.

80:1–50:1–30:1–10:1) to give the TES ether **3** (7.9 g, 68%) as a white foam. Mp: 86–89 °C, TLC R_f = 0.76 (PE/acetone = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 5.08 (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), 3.88 (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), 3.12 (dd, *J* = 9.7, 7.0 Hz, 1H), 2.88–2.86 (m, 1H), 2.54–2.50 (m, 1H), 2.38 (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), 1.68 (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, 10*H*), 0.82 (t, *J* = 7.4 Hz, 3H), 0.71–0.54 (m, 18H); MS (ESI) *m/z* calcd for $C_{56}H_{115}NO_{13}Si_3$ $[M + 2H]^{2+}$/2: 546.9, found: 547.4.

*5.1.1.5. Ring-opening intermediate with secondary amine (**6**).* To a solution of **3** (2 g, 1.83 mmol) in anhydrous $CHCl_3$ (20 mL) was added Pb $(OAc)_4$ (0.97 g, 2.19 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h under nitrogen atmosphere. The aldehyde **4** was obtained in a high yield and was directly used in the next step without purification.

Then, ethanolamine **5** (224 mg, 3.67 mmol) and $NaBH(OAc)_3$ (1.16 g, 5.47 mmol) were added to a solution of **4** at 0 °C. The reaction mixture was stirred at room temperature for 4 h and then quenched with saturated $NaHCO_3$ solution (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1) to obtain the crude secondary amine **6** (1.5 g, 72% in two steps from intermediate **3**) as a colorless oil.

*5.1.1.6. Ring-opening intermediate with carboxylic acid (**9a**).* NaBH $(OAc)_3$ (369 mg, 1.74 mmol) and **7a** (233 mg, 1.16 mmol) were added to a solution of **6** (660 mg, 0.58 mmol) in anhydrous $CHCl_3$ (20 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 30:1:0.1) to obtain the crude ester **8a** as a colorless oil.

LiOH (69 mg, 2.9 mmol) was added to a solution of **8a** in the mixed solvents of THF (15 mL), EtOH (5 mL) and H_2O (5 mL) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was evaporated *in vacuo* and the residue was separated chromatographically (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 15:1:0.1 ~ 10:1:0.1) to afford the carboxylic acid **9a** (0.4 g, 55% in two steps from intermediate **6**) as a colorless oil. TLC R_f = 0.51 (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.91–7.79 (m, 3H), 7.44–7.39 (m, 2H), 7.33 (dd, *J* = 14.7, 7.4 Hz, 1H), 5.41–5.34 (m, 1H), 4.80 (dd, *J* = 32.1, 4.6 Hz, 1H), 4.66–4.55 (m, 1H), 4.53–4.38 (m, 2H), 4.31–4.22 (m, 1H), 3.97 (s, 1H), 3.74 (d, *J* = 6.1 Hz, 1H), 3.65–3.58 (m, 1H), 3.30–3.18 (m, 10H), 3.03 (s, 1H), 2.81–2.71 (m, 2H), 2.68–2.59 (m, 3H), 2.53–2.42 (m, 3H), 2.36–2.15 (m, 10H), 2.04–2.00 (m, 2H), 1.84–1.75 (m, 1H), 1.69–1.61 (m, 2H), 1.49–1.45 (m, 1H), 1.25–1.23 (m, 17H), 1.17 (d, *J* = 4.6 Hz, 3H), 1.08 (d, *J* = 7.4 Hz, 3H), 0.99–0.88 (m, 30H), 0.69–0.58 (m, 18H); MS (ESI) *m/z* calcd for $C_{64}H_{122}N_5O_{12}Si_3$ $[M + H]^+$: 1236.8, $[M + 2H]^{2+}$/2: 618.9, found: 1237.2, 619.5.

*5.1.1.7. 15-Membered 11a-homo-aza-clarithromycin intermediate (**10a**).* To a suspension of **9a** (400 mg, 0.32 mmol) and Et_3N (324 mg, 3.2 mmol) in THF (5 mL) was added 2,4,6-trichlorobenzoyl chloride (234 mg, 0.96 mmol) at room temperature. The reaction solution was stirred at room temperature for 4 h under nitrogen atmosphere. DMAP (985 mg, 8 mmol) and CH_3CN (30 mL) were added to the reaction solution, and refluxed for 0.5 h. The reaction mixture was concentrated *in vacuo* to dryness, and then added DCM (20 mL) and saturated NH_4Cl solution (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (PE/acetone = 15:1 ~ 10:1) to obtain the cyclic intermediate **10a** (250 mg, 63%) as a colorless oil. TLC R_f = 0.54 (PE/acetone = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.87–7.74 (m, 3H), 7.44–7.41 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 5.38–5.32 (m, 1H), 4.78–4.69 (m, 1H), 4.54–4.45 (m, 3H), 4.32–4.13 (m, 2H), 4.12–4.01 (m, 1H), 3.70–3.63 (m, 1H), 3.30–3.09 (m, 9H), 2.85–2.74 (m, 2H), 2.74–2.56 (m, 3H), 2.56–2.38 (m, 4H), 2.23–2.01 (m, 9H), 1.87–1.79 (m, 1H), 1.62–1.61 (m, 5H), 1.32 (s, 3H), 1.22–1.15 (m, 17H), 0.99–0.87 (m, 33H), 0.80–0.57 (m, 18H); MS (ESI) *m/z* calcd for $C_{64}H_{120}N_5O_{11}Si_3$ $[M + H]^+$: 1218.8, $[M + 2H]^{2+}$/2: 609.9, found: 1219.1, 610.4.

*5.1.1.8. 11-N-{[3-(4-Phenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin (**11a**).* Hydrogen fluoride–pyridine (56 mg, 0.37 mmol, 65%) was added to a solution of **10a** (150 mg, 0.12 mmol) in THF (5 mL) at room temperature, and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL) and diluted with DCM (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1) to give compound **11a** (50 mg, 46%) as a white solid. Mp: 84–86 °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): 7.90 (s, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.44–7.41 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 4.88 (d, *J* = 4.6 Hz, 1H), 4.48–4.44 (m, 3H), 4.38 (s, 1H), 4.10 (s, 1H), 4.06–4.01 (m, 1H), 3.92 (d, *J* = 11.7 Hz, 1H), 3.75 (d, *J* = 7.5 Hz, 1H), 3.57–3.48 (m, 2H), 3.34–3.19 (m, 8H), 3.02 (t, *J* = 8.6 Hz, 2H), 2.87–2.84 (m, 1H), 2.72–2.51 (m, 5H), 2.47–2.15 (m, 14H), 1.94–1.91 (m, 1H), 1.71–1.66 (m, 2H), 1.46–1.42 (m, 1H), 1.34 (s, 3H), 1.30–1.25 (m, 10H), 1.19–1.18 (m, 3H), 1.09–1.07 (m, 3H), 0.89–0.87 (m, 3H), 0.79 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.74, 147.70, 130.71, 128.82, 128.79, 128.06, 125.75, 125.72, 120.14, 103.33, 96.28, 80.51, 78.10, 72.73, 72.71, 71.01, 68.85, 68.20, 65.52, 65.36, 52.48, 50.33, 49.49, 48.18, 45.21, 40.34, 39.39, 35.06, 34.11, 31.83, 29.31, 28.04, 27.21, 25.74, 23.49, 22.61, 21.60, 21.40, 18.31, 14.08, 13.99, 10.38; HRMS (ESI) *m/z* calcd for $C_{46}H_{78}N_5O_{11}$ $[M + H]^+$: 876.5698, $[M + 2H]^{2+}$/2: 438.7888, found: 876.5691, 438.8012.

According to the synthetic procedure of compound **11a**, the other compounds (**11b**-**11**) in Series A were also prepared.

*5.1.1.9. 11-N-{[3-(4-p-Methylphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin (**11b**).* White solid, yield 55%, mp: 90–92 °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 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.88 (d, *J* = 4.8 Hz, 1H), 4.56–4.36 (m, 5H), 4.08 (s, 1H), 4.03–4.01 (m, 1H), 3.91 (d, *J* = 12.0 Hz, 1H), 3.75 (d, *J* = 7.2 Hz, 1H), 3.54 (s, 2H), 3.34–3.16 (m, 8H), 3.03 (t, *J* = 8.7 Hz, 1H), 2.95–2.91 (m, 1H), 2.86–2.84 (m, 1H), 2.73–2.52 (m, 5H), 2.46–2.05 (m, 17H), 1.91 (s, 1H), 1.58 (d, *J* = 5.0 Hz, 2H), 1.56–1.55 (m, 1H), 1.33 (s, 3H), 1.28–1.25 (m, 10H), 1.18 (d, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.69, 147.78, 137.91, 129.48, 127.85, 125.65, 119.76, 103.14, 96.24, 80.44, 79.48, 78.23, 78.06, 72.76, 71.01, 68.68, 65.59, 65.34, 53.22, 52.47, 50.33, 49.49, 48.17, 45.14, 36.62, 35.03, 34.03, 29.70, 29.32, 27.99, 27.22, 25.55, 22.69, 21.60, 21.32, 21.29, 18.32, 14.05, 10.42; HRMS (ESI) *m/z* calcd for $C_{47}H_{80}N_5O_{11}$ $[M + H]^+$: 890.5854, $[M + 2H]^{2+}$/2: 445.7967, found: 890.5858, 445.8036.

*5.1.1.10. 11-N-{[3-(4-p-Ethylphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin (**11c**).* White solid, yield 43%, mp: 96–98 °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 (s, 1H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.25 (s, 2H), 4.88 (d, $J = 4.5$ Hz, 1H), 4.46–4.42 (m, 4H), 4.08 (s, 1H), 4.03–4.00 (m, 1H), 3.91 (d, $J = 12.0$ Hz, 1H), 3.75 (d, $J = 7.1$ Hz, 1H), 3.55 (s, 2H), 3.31–3.21 (m, 8H), 3.06–3.02 (m, 2H), 2.86–2.84 (m, 1H), 2.70–2.60 (m, 7H), 2.43–2.10 (m, 14H), 1.92 (s, 1H), 1.67–1.66 (m, 2H), 1.56–1.55 (m, 1H), 1.33 (s, 3H), 1.28–1.25 (m, 13H), 1.18 (d, $J = 7.3$ Hz, 3H), 1.07 (d, $J = 7.1$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 3H), 0.78 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 175.62, 147.56, 138.14, 129.48, 127.45, 125.49, 120.27, 102.09, 96.30, 80.13, 80.04, 78.49, 77.70, 72.80, 70.93, 68.20, 68.01, 67.88, 65.89, 65.16, 62.59, 61.45, 50.48, 49.29, 44.49, 35.03, 29.61, 29.23, 21.45, 21.21, 20.88, 18.77, 18.21, 14.69, 10.51; MS (ESI) *m/z* calcd for $C_{48}H_{82}N_5O_{11}$ $[M + H]^+$: 904.6, $[M + 2H]^{2+}/2$: 452.8, found: 904.8, 453.2.

5.1.1.11. 11-N-{[3-(4-p-n-Propylphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin ***(11d)***. White solid, yield 41%, mp: 78–80 °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 (s, 1H), 7.73 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 4.88 (d, $J = 4.4$ Hz, 1H), 4.50–4.39 (m, 5H), 4.07 (s, 1H), 4.03–4.00 (m, 1H), 3.91 (d, $J = 12.1$ Hz, 1H), 3.75 (d, $J = 7.0$ Hz, 1H), 3.60–3.53 (m, 2H), 3.34–3.28 (m, 4H), 3.22–3.20 (m, 4H), 3.03 (s, 2H), 2.86–2.84 (m, 1H), 2.70–2.60 (m, 7H), 2.45–2.11 (m, 14H), 1.92–1.90 (m, 1H), 1.68–1.65 (m, 4H), 1.56 (d, $J = 4.9$ Hz, 1H), 1.32 (s, 3H), 1.27–1.26 (m, 10H), 1.18 (d, $J = 7.3$ Hz, 3H), 1.06 (d, $J = 7.3$ Hz, 3H), 0.95 (t, $J = 7.3$ Hz, 3H), 0.86 (d, $J = 7.1$ Hz, 3H), 0.78 (d, $J = 6.4$ Hz, 3H); MS (ESI) *m/z* calcd for $C_{49}H_{84}N_5O_{11}$ $[M + H]^+$: 918.6, $[M + 2H]^{2+}/2$: 459.8, found: 918.9, 460.2.

5.1.1.12. 11-N-{[3-(4-p-Tert-butylphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin ***(11e)***. White solid, yield 49%, mp: 110–112 °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): 7.84 (s, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.4$ Hz, 2H), 4.88 (d, $J = 4.5$ Hz, 1H), 4.54–4.36 (m, 5H), 4.08–4.00 (m, 2H), 3.91 (d, $J = 12.0$ Hz, 1H), 3.75 (d, $J = 7.1$ Hz, 1H), 3.57–3.51 (m, 2H), 3.34–3.19 (m, 8H), 3.08–2.98 (m, 2H), 2.86–2.84 (m, 1H), 2.70–2.53 (m, 5H), 2.45–2.04 (m, 14H), 1.94–1.90 (m, 1H), 1.58–1.55 (m, 3H), 1.35–1.33 (m, 12H), 1.29–1.25 (m, 10H), 1.18 (d, $J = 7.3$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.79 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.54, 151.11, 147.63, 127.78, 125.64, 125.62, 125.41, 125.38, 119.71, 119.65, 103.02, 96.17, 80.36, 79.53, 78.18, 77.97, 72.71, 70.94, 68.55, 65.55, 65.29, 53.18, 52.43, 50.25, 49.39, 48.10, 45.05, 36.58, 34.97, 34.57, 33.94, 31.21, 29.61, 27.91, 27.13, 21.51, 21.20, 18.34, 18.24, 14.02, 13.97, 11.84, 10.35; MS (ESI) *m/z* calcd for $C_{50}H_{86}N_5O_{11}$ $[M + H]^+$: 932.6, $[M + 2H]^{2+}/2$: 466.8, found: 932.8, 467.2.

5.1.1.13. 11-N-{[3-(4-p-n-Butylphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin ***(11f)***. White solid, yield 36%, mp: 94–96 °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): 7.85 (s, 1H), 7.74 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 4.88 (d, $J = 4.6$ Hz, 1H), 4.46–4.44 (m, 3H), 4.37 (t, $J = 10.3$ Hz, 1H), 4.10 (s, 1H), 4.04 (dd, $J = 9.0$, 6.4 Hz, 1H), 3.92 (d, $J = 12.1$ Hz, 1H), 3.75 (d, $J = 7.2$ Hz, 1H), 3.52 (s, 2H), 3.35–3.20 (m, 8H), 3.02–3.01 (m, 1H), 2.90–2.83 (m, 2H), 2.65–2.62 (m, 2H), 2.58–2.06 (m, 19H), 1.92–1.91 (m, 1H), 1.70–1.68 (m, 2H), 1.63–1.61 (m, 2H), 1.54 (d, $J = 4.8$ Hz, 1H), 1.40–1.36 (m, 2H), 1.34 (s, 3H), 1.30–1.25 (m, 10H), 1.18 (d, $J = 7.3$ Hz, 3H), 1.09 (d, $J = 7.1$ Hz, 3H), 0.94 (t, $J = 7.4$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.79 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ 176.42, 147.62, 142.74, 128.63, 127.91, 125.47, 119.53, 103.01, 96.08, 80.28, 79.27, 78.35, 78.07, 77.89, 72.57, 70.84, 68.52, 65.39, 65.20, 61.64, 60.39, 53.11, 52.34, 50.12, 49.27, 47.97, 44.98, 40.84, 40.22, 36.48, 35.22, 34.89, 33.87, 33.33, 27.82, 22.11, 21.38, 21.13, 18.12, 13.80, 13.72, 10.20; MS (ESI) *m/z* calcd for $C_{50}H_{86}N_5O_{11}$ $[M + H]^+$: 932.6, $[M + 2H]^{2+}/2$: 466.8, found: 932.8, 467.1.

5.1.1.14. 11-N-{[3-(4-p-n-Amylphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin ***(11g)***. White solid, yield 32%, mp: 97–99 °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): 7.85 (s, 1H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 4.88 (d, $J = 4.5$ Hz, 1H), 4.46–4.44 (m, 4H), 4.09–4.01 (m, 2H), 3.92 (d, $J = 11.9$ Hz, 1H), 3.75 (d, $J = 7.4$ Hz, 1H), 3.53 (s, 2H), 3.39–3.14 (m, 8H), 3.03–3.01 (m, 1H), 2.91–2.84 (m, 2H), 2.72–2.02 (m, 21H), 1.93–1.91 (m, 1H), 1.65–1.63 (m, 4H), 1.55 (d, $J = 4.8$ Hz, 1H), 1.38–1.32 (m, 7H), 1.29–1.25 (m, 10H), 1.18 (d, $J = 7.3$ Hz, 3H), 1.08 (d, $J = 6.5$ Hz, 3H), 0.91–0.87 (m, 6H), 0.79 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ 176.43, 147.62, 142.77, 128.63, 127.91, 125.47, 119.54, 103.04, 96.09, 80.29, 79.24, 78.08, 77.90, 72.57, 70.85, 68.55, 65.38, 65.20, 61.64, 60.36, 53.12, 52.35, 50.12, 49.28, 47.97, 44.99, 40.86, 40.21, 36.48, 35.51, 34.89, 33.88, 31.26, 30.85, 29.48, 27.83, 22.32, 21.38, 21.14, 18.12, 13.80, 10.20; MS (ESI) *m/z* calcd for $C_{51}H_{88}N_5O_{11}$ $[M + H]^+$: 946.6, $[M + 2H]^{2+}/2$: 473.8, found: 947.0, 474.0.

5.1.1.15. 11-N-{[3-(4-p-Methoxyphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin ***(11h)***. White solid, yield 80%, mp: 85–87 °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): 7.80 (s, 1H), 7.75 (d, $J = 8.7$ Hz, 2H), 6.96 (d, $J = 8.7$ Hz, 2H), 4.88 (d, $J = 4.4$ Hz, 1H), 4.47–4.41 (m, 4H), 4.08 (s, 1H), 4.03–3.99 (m, 1H), 3.91 (d, $J = 12.2$ Hz, 1H), 3.85 (s, 3H), 3.75 (d, $J = 7.2$ Hz, 1H), 3.59–3.50 (m, 2H), 3.39–3.16 (m, 8H), 3.03 (s, 1H), 2.94–2.92 (m, 1H), 2.86–2.84 (m, 1H), 2.71–2.53 (m, 5H), 2.48–1.97 (m, 14H), 1.94–1.90 (m, 1H), 1.68–1.66 (m, 2H), 1.55 (d, $J = 4.8$ Hz, 1H), 1.32 (s, 3H), 1.29–1.25 (m, 10H), 1.18 (d, $J = 7.3$ Hz, 3H), 1.06 (d, $J = 7.1$ Hz, 3H), 0.86 (d, $J = 7.1$ Hz, 3H), 0.78 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): δ 176.55, 159.49, 147.48, 126.95, 123.36, 119.22, 114.14, 102.99, 96.15, 80.34, 79.51, 78.41, 78.16, 77.96, 72.70, 70.92, 68.53, 65.53, 65.28, 55.23, 53.14, 52.40, 50.23, 49.39, 48.07, 45.04, 40.36, 36.58, 34.96, 33.90, 29.59, 29.22, 27.90, 27.12, 22.58, 21.49, 21.19, 18.23, 13.97, 10.33; MS (ESI) *m/z* calcd for $C_{47}H_{80}N_5O_{12}$ $[M + H]^+$: 906.6, $[M + 2H]^{2+}/2$: 453.8, found: 906.8, 454.2.

5.1.1.16. 11-N-{[3-(4-p-Ethoxyphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin ***(11i)***. White solid, yield 58%, mp: 101–103 °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): 7.81 (s, 1H), 7.75 (d, $J = 8.8$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 4.88 (d, $J = 4.6$ Hz, 1H), 4.45–4.43 (m, 3H), 4.36 (t, $J = 10.2$ Hz, 1H), 4.11–4.03 (m, 4H), 3.92 (d, $J = 12.0$ Hz, 1H), 3.75 (d, $J = 7.6$ Hz, 1H), 3.55–3.49 (m, 2H), 3.35–3.20 (m, 8H), 3.02 (t, $J = 7.6$ Hz, 1H), 2.92–2.84 (m, 2H), 2.69–2.47 (m, 5H), 2.47–2.10 (m, 14H), 1.92–1.91 (m, 1H), 1.70–1.66 (m, 2H), 1.54 (d, $J = 4.9$ Hz, 1H), 1.43 (t, $J = 7.0$ Hz, 3H), 1.34 (s, 3H), 1.30–1.24 (m, 10H), 1.18 (d, $J = 7.3$ Hz, 3H), 1.09 (d, $J = 7.3$ Hz, 3H), 0.87 (d, $J = 7.1$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 176.43, 158.73, 147.41, 126.81, 123.11, 119.05, 114.58, 103.01, 96.06, 80.27, 79.22, 78.33, 78.05, 77.87, 72.56, 70.83, 68.52, 65.36, 65.17, 63.30, 61.61, 60.36, 53.07, 52.32, 50.10, 49.26, 47.93, 44.97, 40.85, 40.20, 36.46, 34.87, 33.84, 31.28, 29.49, 27.79, 21.37, 21.12, 18.10, 14.60, 13.79, 10.17; MS (ESI) *m/z* calcd for $C_{48}H_{82}N_5O_{12}$ $[M + H]^+$: 920.6, $[M + 2H]^{2+}/2$: 460.8, found: 920.8, 461.2.

5.1.1.17. 11-N-{[3-(4-p-Propoxyphenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin ***(11j)***. White solid, yield 61%, mp: 87–89 °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): 7.80 (s, 1H), 7.74 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 4.88 (d, $J = 4.7$ Hz, 1H), 4.45–4.43 (m, 3H), 4.39–4.36 (m, 1H), 4.10–4.02 (m, 2H), 3.96 (t, $J = 6.6$ Hz, 2H), 3.93–3.91 (m, 1H), 3.75 (d, $J = 7.5$ Hz, 1H), 3.52 (s, 2H), 3.33–3.20 (m, 8H), 3.02 (t, $J = 7.9$ Hz, 1H), 2.93–2.89 (m, 1H), 2.87–2.84 (m, 1H), 2.70–2.51 (m, 5H), 2.49–2.09 (m, 14H), 1.93–1.91 (m, 1H), 1.85–1.81 (m, 2H), 1.67–1.64

(m, 2H), 1.55 (d, J = 4.8 Hz, 1H), 1.34 (s, 3H), 1.30–1.24 (m, 10H), 1.18 (d, J = 7.3 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.87 (d, J = 7.1 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 176.42, 158.94, 147.42, 126.79, 123.06, 119.04, 114.61, 103.04, 96.06, 80.27, 79.19, 78.34, 78.05, 77.88, 72.55, 70.84, 69.39, 68.53, 65.35, 65.17, 60.33, 53.08, 52.34, 50.08, 49.25, 47.92, 44.98, 40.86, 40.17, 36.48, 34.88, 33.85, 29.40, 27.79, 22.37, 21.36, 21.13, 18.10, 13.76, 10.27, 10.16; MS (ESI) *m/z* calcd for $C_{49}H_{84}N_5O_{12}$ $[M + H]^+$: 934.6, $[M + 2H]^{2+}/2$: 467.8, found: 934.9, 468.1.

*5.1.1.18. 11-N-{[3-(4-p-Fluorophenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin (**11k**).* White solid, yield 35%, mp: 85–87 °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): 7.86–7.78 (m, 3H), 7.14–7.10 (m, 2H), 4.88 (d, J = 4.7 Hz, 1H), 4.49–4.46 (m, 4H), 4.05 (s, 1H), 4.00–3.97 (m, 1H), 3.91 (d, J = 12.2 Hz, 1H), 3.74 (d, J = 2.7 Hz, 1H), 3.60–3.55 (m, 2H), 3.36–3.10 (m, 8H), 3.04 (s, 1H), 2.99–2.94 (m, 1H), 2.91–2.71 (m, 6H), 2.62–1.98 (m, 14H), 1.91 (s, 1H), 1.65–1.63 (m, 2H), 1.57 (d, J = 4.8 Hz, 1H), 1.31 (s, 3H), 1.29–1.26 (m, 10H), 1.18 (d, J = 7.3 Hz, 3H), 1.03 (d, J = 7.3 Hz, 3H), 0.86 (d, J = 8.4 Hz, 3H), 0.82–0.75 (m, 3H); MS (ESI) *m/z* calcd for $C_{46}H_{77}FN_5O_{11}$ $[M + H]^+$: 894.6, $[M + 2H]^{2+}/2$: 447.8, found: 894.8, 448.2.

*5.1.1.19. 11-N-{[3-(4-p-Chlorophenyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin (**11l**).* White solid, yield 46%, mp: 84–86 °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): 7.90 (s, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 4.88 (d, J = 4.7 Hz, 1H), 4.52–4.41 (m, 4H), 4.05 (s, 1H), 3.99 (dd, J = 9.1, 6.3 Hz, 1H), 3.92 (d, J = 12.3 Hz, 1H), 3.75 (d, J = 6.6 Hz, 1H), 3.62–3.55 (m, 2H), 3.33–3.20 (m, 8H), 3.05–3.00 (m, 2H), 2.99–2.95 (m, 1H), 2.87–2.73 (m, 5H), 2.36–2.00 (m, 14H), 1.91 (s, 1H), 1.68 (s, 2H), 1.56 (s, 1H), 1.31 (s, 3H), 1.27–1.25 (m, 10H), 1.18 (d, J = 7.3 Hz, 3H), 1.02 (d, J = 7.4 Hz, 3H), 0.87 (d, J = 7.3 Hz, 3H), 0.81–0.75 (m, 3H); MS (ESI) *m/z* calcd for $C_{46}H_{77}ClN_5O_{11}$ $[M + H]^+$: 910.5, $[M + 2H]^{2+}/2$: 455.8, found: 910.8, 456.2.

*5.1.1.20. 11-N-{[3-(4-o-Pyridyl-1H-1,2,3-triazol-1-yl)-1-yl]propyl}-9(S)-hydroxyclarithromycin (**11m**).* White solid, yield 39%, mp: 96–98 °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): 8.58 (d, J = 4.7 Hz, 1H), 8.22 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.78 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 4.9 Hz, 1H), 4.88 (d, J = 4.7 Hz, 1H), 4.54–4.45 (m, 4H), 4.38–4.35 (m, 1H), 4.08–4.01 (m, 2H), 3.92 (d, J = 12.1 Hz, 1H), 3.75 (d, J = 7.2 Hz, 1H), 3.58–3.48 (m, 2H), 3.34–3.20 (m, 8H), 3.02 (d, J = 8.8 Hz, 1H), 2.89–2.84 (m, 2H), 2.63–2.52 (m, 5H), 2.39–2.05 (m, 14H), 1.91 (s, 1H), 1.71 (dd, J = 13.9, 7.2 Hz, 2H), 1.57–1.55 (m, 1H), 1.33 (s, 3H), 1.28–1.24 (m, 10H), 1.19 (d, J = 7.3 Hz, 3H), 1.07 (d, J = 7.4 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 176.42, 150.06, 149.11, 148.06, 136.67, 122.57, 122.12, 119.99, 102.76, 95.96, 80.17, 79.37, 78.23, 78.04, 77.82, 72.57, 70.78, 68.24, 65.38, 65.03, 60.17, 52.33, 50.07, 49.23, 48.22, 44.85, 40.21, 36.49, 34.81, 33.79, 30.20, 29.43, 27.73, 21.33, 21.01, 18.09, 13.82, 10.10; MS (ESI) *m/z* calcd for $C_{45}H_{77}N_6O_{11}$ $[M + H]^+$: 877.6, $[M + 2H]^{2+}/2$: 439.3, found: 877.8, 439.7.

5.1.2. Synthesis of C13-substituted 15-membered homoclarithromycin derivatives (Series B)

*5.1.2.1. (R)-1-Azido-3-chloropropan-2-ol (**22**).* To a solution of *R*-epichlorohydrin **21** (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 stirred at 30 °C for 5 h, and then EtOAc (20 mL) was added. The organic phase was separated and aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. Purification using column chromatography (PE/EtOAc = 6:1) yielded azide **22** (1.27 g, 86%) as a light yellow oil.

*5.1.2.2. (R)-1-Chloro-3-[4-(p-tolyl)-1H-1,2,3-triazol-1-yl]propan-2-ol (**24**).* **22** (0.35 g, 2.58 mmol) in 75% methanol solution (20 mL) was reacted with 4-ethynyltoluene **23** (0.25 g, 2.15 mmol) in the presence of $CuSO_4$ (22 mg) and L-ascorbic acid sodium salt (66 mg) at 40 °C for 24 h. The reaction mixture was evaporated *in vacuo* and the residue was separated chromatographically (DCM/CH_3OH = 30:1) to form the alcohol **24** (0.51 g, 94%) as a white solid. Mp: 118–120 °C, TLC R_f = 0.32 (DCM/CH_3OH = 30:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.83 (s, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 4.67 (dd, J = 14.0, 3.4 Hz, 1H), 4.50 (dd, J = 14.0, 7.0 Hz, 1H), 4.42–4.38 (m, 1H), 3.61–3.60 (m, 2H), 2.38 (s, 3H); MS (ESI) *m/z* calcd for $C_{12}H_{15}ClN_3O$ $[M + H]^+$: 252.1, found: 252.2.

*5.1.2.3. (S)-1-Amino-[3-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl]propan-2-ol (**16a**).* NaOH solution (5 mL, 10 M) was added to a solution of alcohol **24** (0.5 g, 1.99 mmol) in CH_3CN (2 mL) and stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to yield the epoxide **25** as a white solid. This intermediate **25** can be used directly in the next step without purification.

25% $NH_3{\cdot}H_2O$ solution (20 mL) was added to a solution of the epoxide **25** in CH_3CN (2 mL) and stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. Purification by column chromatography ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 10:1:0.1) afforded substituted ethanolamine **16a** (0.27 g, 58% in two steps from intermediate **24**) as a white solid. Mp: 135–137 °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): 8.42 (s, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.12 (s, 1H), 4.49 (dd, J = 13.8, 4.0 Hz, 1H), 4.29–4.25 (m, 1H), 3.80–3.76 (m, 1H), 2.57–2.53 (m, 2H), 2.33 (s, 3H), 1.63 (s, 2H); MS (ESI) *m/z* calcd for $C_{12}H_{17}N_4O$ $[M + H]^+$: 233.1, found: 233.3.

*5.1.2.4. Ring-opening intermediate with carboxylic acid (**18a**).* To a solution of **3** (469 mg, 0.43 mmol) in anhydrous $CHCl_3$ (20 mL) was added $Pb(OAc)_4$ (228 mg, 0.52 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h under nitrogen atmosphere. The aldehyde **4** was obtained in a high yield and was directly used in the next step without purification.

To a solution of **4** was added **16a** (200 mg, 0.86 mmol) and $NaBH(OAc)_3$ (273 mg, 1.29 mmol) at 0 °C . The reaction mixture was stirred at room temperature for 4 h under nitrogen atmosphere. Then, $NaBH(OAc)_3$ (273 mg, 1.29 mmol) and 37% aqueous formaldehyde solution (209 mg, 2.58 mmol) were added and stirred at room temperature for another 4 h under nitrogen atmosphere. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 30:1:0.1) to yield the crude ester **17a** as a colorless oil.

LiOH (51 mg, 2.15 mmol) was added to a solution of **17a** in the mixed solvents of THF (15 mL), EtOH (5 mL) and H_2O (5 mL) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was evaporated *in vacuo* and the residue was separated chromatographically ($DCM/CH_3OH/NH_3{\cdot}H_2O$ = 15:1:0.1 ~ 10:1:0.1) to give the carboxylic acid **18a** (0.37 g, 70% in four steps from intermediate **3**) as a white solid. Mp: 89–92 °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): 7.99 (s, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 4.79 (d, J = 4.6 Hz,

1H), 4.55 (dd, J = 13.8, 4.0 Hz, 1H), 4.48–4.41 (m, 3H), 4.26 (dd, J = 9.0, 6.4 Hz, 1H), 3.93–3.92 (m, 1H), 3.73 (d, J = 6.0 Hz, 1H), 3.63–3.59 (m, 1H), 3.30 (s, 3H), 3.25–3.16 (m, 7H), 3.07 (d, J = 10.0 Hz, 1H), 2.79 (s, 1H), 2.68–2.64 (m, 1H), 2.58 (s, 3H), 2.39–2.25 (m, 8H), 2.19 (s, 6H), 1.79–1.74 (m, 1H), 1.62–1.55 (m, 2H), 1.45 (dd, J = 15.0, 4.9 Hz, 1H), 1.28 (s, 3H), 1.27–1.25 (m, 1H), 1.22 (d, J = 6.3 Hz, 3H), 1.18–1.14 (m, 10H), 1.11 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 7.4 Hz, 3H), 0.98–0.91 (m, 30H), 0.67–0.57 (m, 18H); MS (ESI) *m/z* calcd for $C_{64}H_{123}N_5O_{12}Si_3$ $[M + 2H]^{2+}$/2: 618.9, found: 619.5.

*5.1.2.5. 15-Membered 11a-homo-aza-clarithromycin intermediate (**19a**).* **18a** (370 mg, 0.30 mmol), Et_3N (303 mg, 3 mmol) and 2,4,6-trichlorobenzoyl chloride (219 mg, 0.9 mmol) were added in THF (5 mL) at room temperature. The reaction solution was stirred at room temperature for 4 h under nitrogen atmosphere. DMAP (922 mg, 7.5 mmol) and CH_3CN (30 mL) were added to the reaction solution, and refluxed for 0.5 h. The reaction mixture was concentrated *in vacuo* to dryness, and then DCM (20 mL) and saturated NH_4Cl solution (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 anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (PE/acetone = 15:1 ~ 10:1) to afford the cyclic intermediate **19a** (150 mg, 41%) as a white solid. Mp: 85–88 °C, TLC R_f = 0.53 (PE/acetone = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.72–7.70 (m, 3H), 7.23 (d, J = 8.0 Hz, 2H), 5.25 (s, 1H), 4.81–4.76 (m, 1H), 4.72–4.69 (m, 1H), 4.57–4.52 (m, 1H), 4.39 (d, J = 6.9 Hz, 1H), 4.27–4.17 (m, 2H), 3.65–3.62 (m, 1H), 3.57–3.53 (m, 1H), 3.31 (s, 1H), 3.27 (s, 3H), 3.21–3.16 (m, 5H), 2.79–2.73 (m, 2H), 2.52–2.42 (m, 3H), 2.38–2.37 (m, 4H), 2.32–2.27 (m, 3H), 2.20 (s, 6H), 2.13–2.10 (m, 1H), 1.96–1.90 (m, 2H), 1.84–1.81 (m, 1H), 1.63–1.61 (m, 2H), 1.37 (d, J = 6.7 Hz, 1H), 1.31 (s, 3H), 1.24–1.22 (m, 4H), 1.16–1.14 (m, 13H), 0.99–0.95 (m, 33H), 0.65–0.59 (m, 18H); MS (ESI) *m/z* calcd for $C_{64}H_{121}N_5O_{11}Si_3$ $[M + 2H]^{2+}$/2: 609.9, found: 610.5.

*5.1.2.6. 13(S)-[1-(4-p-Methylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**20a**).* Hydrogen fluoride–pyridine (56 mg, 0.37 mmol, 65%) was added to **19a** (150 mg, 0.12 mmol) in THF (5 mL) at room temperature, and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL) and diluted with DCM (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (DCM/CH_3OH/$NH_3{\cdot}H_2O$ = 10:1:0.1) to obtain compound **20a** (55 mg, 51%) as a white solid. Mp: 98–100 °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): 7.76–7.70 (m, 3H), 7.24 (d, J = 7.9 Hz, 2H), 5.54–5.52 (m, 1H), 4.81 (d, J = 4.1 Hz, 1H), 4.56 (dd, J = 14.6, 4.5 Hz, 1H), 4.49 (dd, J = 14.5, 5.1 Hz, 1H), 4.43 (d, J = 6.9 Hz, 1H), 4.28 (s, 1H), 4.02–3.97 (m, 1H), 3.72 (d, J = 7.1 Hz, 1H), 3.55–3.49 (m, 2H), 3.26 (s, 3H), 3.22–3.04 (m, 5H), 3.02–2.93 (m, 2H), 2.93–2.89 (m, 1H), 2.79–2.58 (m, 5H), 2.58–2.24 (m, 12H), 2.21–2.11 (m, 3H), 1.88–1.85 (m, 1H), 1.81–1.71 (m, 2H), 1.45 (dd, J = 15.1, 4.7 Hz, 1H), 1.29 (s, 3H), 1.28 (d, J = 6.3 Hz, 3H), 1.26–1.18 (m, 10H), 1.01 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 176.14, 148.11, 138.22, 129.58, 127.50, 125.66, 125.63, 120.07, 102.83, 96.19, 80.03, 78.73, 77.99, 72.76, 70.98, 68.34, 65.59, 65.23, 63.05, 59.01, 51.65, 50.17, 49.45, 45.15, 44.18, 34.89, 32.54, 30.73, 21.52, 21.30, 21.10, 21.04, 18.27, 18.21, 14.78, 10.80; HRMS (ESI) *m/z* calcd for $C_{46}H_{78}N_5O_{11}$ $[M + H]^+$: 876.5698, $[M + 2H]^{2+}$/2: 438.7880, found: 876.5699, 438.7960.

According to the synthetic procedure of compound **20a**, the other compounds (**20b**-**20 l**) in Series B were also prepared.

*5.1.2.7. 13(R)-[1-(4-p-Methylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**20b**).* White solid, yield 63%, mp: 96–99 °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): 7.78–7.70 (m, 3H), 7.23 (d, J = 7.9 Hz, 2H), 5.21 (s, 1H), 4.88–4.78 (m, 1H), 4.67–4.55 (m, 2H), 4.45 (d, J = 7.0 Hz, 1H), 4.11–3.95 (m, 2H), 3.88–3.83 (m, 1H), 3.66–3.51 (m, 2H), 3.34–3.14 (m, 8H), 3.04–2.97 (m, 2H), 2.90–2.86 (m, 1H), 2.82–2.54 (m, 5H), 2.54–2.18 (m, 12H), 2.15–2.02 (m, 2H), 1.94–1.91 (m, 1H), 1.80 (s, 1H), 1.67–1.61 (m, 2H), 1.53 (dd, J = 14.4, 3.8 Hz, 1H), 1.39–1.20 (m, 16H), 1.13 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 180.13, 147.95, 138.13, 129.54, 127.61, 125.72, 125.66, 120.07, 96.48, 80.43, 77.73, 72.68, 70.98, 68.41, 66.35, 65.81, 65.40, 65.35, 51.47, 51.37, 50.02, 49.43, 49.39, 40.52, 35.21, 34.83, 30.44, 21.62, 21.45, 21.29, 21.23, 21.14, 20.97, 18.68, 18.27, 10.27; HRMS (ESI) *m/z* calcd for $C_{46}H_{78}N_5O_{11}$ $[M + H]^+$: 876.5698, $[M + 2H]^{2+}$/2: 438.7888, found: 876.5655, 438.7967.

*5.1.2.8. 13(S)-[1-(4-p-Ethylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**20c**).* White solid, yield 36%, mp: 98–100 °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): 7.78–7.73 (m, 3H), 7.27 (s, 2H), 5.54 (s, 1H), 4.79 (d, J = 4.4 Hz, 1H), 4.55–4.54 (m, 1H), 4.46 (d, J = 7.1 Hz, 1H), 4.26 (s, 1H), 4.03–3.89 (m, 2H), 3.72 (d, J = 6.5 Hz, 1H), 3.53–3.46 (m, 2H), 3.32 (s, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 3.11–3.07 (m, 1H), 3.02–2.97 (m, 2H), 2.92–2.89 (m, 1H), 2.82–2.66 (m, 7H), 2.48–2.15 (m, 9H), 2.13–1.97 (m, 3H), 1.88–1.85 (m, 1H), 1.82–1.73 (m, 2H), 1.46–1.45(m, 1H), 1.29–1.25 (m, 16H), 1.19 (d, J = 7.5 Hz, 3H), 0.98 (d, J = 5.5 Hz, 3H), 0.84 (d, J = 4.2 Hz, 3H), 0.72 (d, J = 6.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 175.97, 148.03, 144.52, 128.29, 127.63, 125.67, 125.64, 102.37, 96.17, 79.88, 77.85, 74.18, 72.72, 70.81, 70.76, 67.91, 65.59, 65.16, 51.52, 50.12, 49.34, 44.93, 43.98, 37.22, 34.81, 32.37, 28.57, 21.52, 21.41, 21.37, 21.09, 20.96, 20.85, 19.67, 18.54, 18.19, 17.89, 15.93, 15.41, 14.75, 12.20, 10.72; MS (ESI) *m/z* calcd for $C_{47}H_{80}N_5O_{11}$ $[M + H]^+$: 890.6, $[M + 2H]^{2+}$/2: 445.8, found: 890.8, 446.2.

*5.1.2.9. 13(R)-[1-(4-p-Ethylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**20d**).* White solid, yield 55%, mp: 100–103 °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): 7.74 (dd, J = 13.1, 6.3 Hz, 3H), 7.25 (s, 2H), 5.20 (s, 1H), 4.82 (s, 1H), 4.66–4.58 (m, 2H), 4.44 (d, J = 7.1 Hz, 1H), 4.04–4.01 (m, 1H), 3.83 (s, 1H), 3.61–3.49 (m, 2H), 3.33 (s, 1H), 3.24 (s, 3H), 3.19 (s, 3H), 3.14 (s, 1H), 3.00–2.96 (m, 2H), 2.90–2.87 (m, 1H), 2.81–2.58 (m, 7H), 2.55–2.33 (m, 9H), 2.26–2.19 (m, 2H), 2.08–2.07 (m, 1H), 1.94–1.91 (m, 1H), 1.84–1.76 (m, 2H), 1.54–1.51 (m, 1H), 1.30–1.19 (m, 19H), 1.14 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.59, 147.62, 144.20, 128.06, 127.63, 125.49, 119.93, 96.25, 80.15, 77.52, 72.43, 70.68, 68.02, 65.97, 65.16, 51.16, 49.78, 49.15, 45.02, 40.23, 40.07, 38.19, 36.88, 34.69, 32.61, 30.14, 29.56, 28.39, 21.30, 20.96, 20.87, 20.79, 18.39, 18.01, 15.23, 9.96; MS (ESI) *m/z* calcd for $C_{47}H_{80}N_5O_{11}$ $[M + H]^+$: 890.6, $[M + 2H]^{2+}$/2: 445.8, found: 890.8, 446.1.

*5.1.2.10. 13(S)-[1-(4-p-n-Propylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**20e**).* White solid, yield 50%, mp: 98–101 °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): 7.73 (d, J = 8.0 Hz, 3H), 7.24 (d, J = 8.0 Hz, 2H), 5.53 (d, J = 9.6 Hz, 1H), 4.83 (d, J = 4.2 Hz, 1H), 4.55–4.54 (m, 1H), 4.49 (dd, J = 14.5, 5.2 Hz, 1H), 4.42 (d, J = 7.1 Hz, 1H), 4.29 (s, 1H), 4.04–3.99 (m, 1H), 3.72 (d, J = 7.4 Hz, 1H), 3.51–3.50 (m, 2H), 3.38–3.20 (m, 8H), 3.04–2.94 (m, 2H), 2.63–2.60 (m, 2H), 2.58–2.43 (m, 5H), 2.38–2.14 (m, 9H), 2.09–2.01 (m, 2H), 1.95–1.75 (m, 4H), 1.69–1.63 (m, 2H), 1.45 (dd, J = 15.2, 4.7 Hz, 1H), 1.30 (s, 3H), 1.28 (d,

J = 6.2 Hz, 3H), 1.25–1.18 (m, 10H), 1.03 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.91, 147.88, 142.76, 128.75, 127.55, 125.40, 119.89, 102.79, 96.00, 79.87, 79.51, 78.61, 77.81, 72.51, 70.75, 68.18, 67.61, 65.31, 65.02, 62.78, 58.83, 51.43, 49.91, 49.19, 44.98, 43.93, 41.06, 40.30, 37.57, 36.65, 34.72, 32.30, 30.74, 24.21, 21.99, 21.28, 20.92, 18.03, 14.47, 13.53, 10.46; MS (ESI) *m/z* calcd for $C_{48}H_{82}N_5O_{11}$ $[M + H]^+$: 904.6, $[M + 2H]^{2+}/2$: 452.8, found: 904.8, 453.1.

5.1.2.11. 13(R)-[1-(4-p-n-Propylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(20f)***. White solid, yield 52%, mp: 90–92 °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): 7.75–7.72 (m, 3H), 7.23 (d, J = 8.1 Hz, 2H), 5.16 (s, 1H), 4.81 (s, 1H), 4.72–4.59 (m, 3H), 4.42 (d, J = 7.2 Hz, 1H), 4.06–4.01 (m, 1H), 3.81 (s, 1H), 3.56–3.46 (m, 2H), 3.32–3.18 (m, 8H), 3.00–2.90 (m, 3H), 2.62–2.60 (m, 2H), 2.57–2.25 (m, 14H), 2.21–2.11 (m, 3H), 1.94–1.91 (m, 1H), 1.83 (s, 2H), 1.68–1.64 (m, 2H), 1.52–1.49 (m, 1H), 1.31–1.22 (m, 16H), 1.15 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 10.1 Hz, 3H), 0.98–0.94 (m, 6H); MS (ESI) *m/z* calcd for $C_{48}H_{82}N_5O_{11}$ $[M + H]^+$: 904.6, $[M + 2H]^{2+}/2$: 452.8, found: 904.8, 453.2.

5.1.2.12. 13(S)-[1-(4-p-n-Amylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(20g)***. White solid, yield 27%, mp: 94–96 °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): 7.73 (d, J = 8.0 Hz, 3H), 7.24 (d, J = 8.2 Hz, 2H), 5.53–5.51 (m, 1H), 4.84–4.83 (m, 1H), 4.56 (dd, J = 14.4, 4.5 Hz, 1H), 4.49 (dd, J = 14.5, 5.2 Hz, 1H), 4.41 (d, J = 6.9 Hz, 1H), 4.30 (s, 1H), 4.03–4.01 (m, 1H), 3.72 (d, J = 7.5 Hz, 1H), 3.50 (d, J = 7.3 Hz, 2H), 3.37–3.16 (m, 8H), 2.99–2.92 (m, 2H), 2.70 (d, J = 12.7 Hz, 1H), 2.64–2.62 (m, 3H), 2.56–2.18 (m, 14H), 2.16–2.08 (m, 2H), 2.01 (d, J = 10.8 Hz, 1H), 1.88–1.85 (m, 1H), 1.75–1.74 (m, 2H), 1.65–1.61 (m, 2H), 1.45 (dd, J = 15.1, 4.6 Hz, 1H), 1.35–1.20 (m, 20H), 1.03 (d, J = 6.3 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.94, 147.89, 143.03, 128.69, 127.53, 125.42, 119.86, 102.95, 96.01, 79.91, 79.39, 78.63, 77.85, 72.49, 70.82, 68.29, 65.29, 64.98, 62.77, 58.86, 51.44, 49.91, 49.20, 45.03, 43.95, 40.22, 35.48, 34.74, 32.31, 31.23, 30.82, 30.33, 22.28, 21.98, 21.29, 20.98, 18.04, 14.46, 13.77, 10.45; MS (ESI) *m/z* calcd for $C_{50}H_{86}N_5O_{11}$ $[M + H]^+$: 932.6, $[M + 2H]^{2+}/2$: 466.8, found: 932.8, 467.3.

5.1.2.13. 13(R)-[1-(4-p-n-Amylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(20h)***. White solid, yield 54%, mp: 102–104 °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): 7.73 (dd, J = 13.8, 7.2 Hz, 3H), 7.23 (d, J = 8.1 Hz, 2H), 5.18 (s, 1H), 4.82 (s, 1H), 4.73–4.58 (m, 3H), 4.43 (d, J = 6.7 Hz, 1H), 4.04–4.02 (m, 1H), 3.82 (s, 1H), 3.59–3.49 (m, 2H), 3.33–3.20 (m, 8H), 2.98–2.86 (m, 3H), 2.64–2.61 (m, 2H), 2.54–2.16 (m, 14H), 2.16–1.94 (m, 3H), 1.94–1.92 (m, 1H), 1.88–1.81 (m, 2H), 1.64–1.62 (m, 2H), 1.54 (s, 1H), 1.35–1.20 (m, 20H), 1.15 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.0 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.52, 147.72, 142.93, 128.64, 127.65, 125.43, 119.84, 103.11, 96.30, 80.17, 79.11, 77.79, 77.63, 72.42, 71.54, 70.84, 68.32, 65.84, 65.18, 51.18, 49.88, 49.19, 45.10, 40.22, 38.14, 36.89, 35.47, 34.83, 32.65, 31.22, 30.83, 30.21, 22.28, 21.32, 21.10, 20.92, 18.39, 13.77, 9.96; MS (ESI) *m/z* calcd for $C_{50}H_{86}N_5O_{11}$ $[M + H]^+$: 932.6, $[M + 2H]^{2+}/2$: 466.8, found: 932.8, 467.2.

5.1.2.14. 13(S)-[1-(4-p-Ethoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(20i)***. White solid, yield 54%, mp: 104–106 °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): 7.74 (d, J = 8.7 Hz, 2H), 7.68 (s, 1H), 6.95 (d, J = 8.7 Hz, 2H), 5.52 (d, J = 9.2 Hz, 1H), 4.82 (s, 1H), 4.55 (dd, J = 14.5, 4.5 Hz, 1H), 4.48 (dd, J = 14.5, 5.1 Hz, 1H), 4.43 (d, J = 6.0 Hz, 1H), 4.29 (s, 1H), 4.09–4.05 (m, 2H), 4.02–4.00 (m, 1H), 3.72 (d, J = 7.2 Hz, 1H), 3.51 (d, J = 8.0 Hz, 2H), 3.35–3.11 (m, 8H), 3.01–2.90 (m, 3H), 2.72–2.68 (m, 2H), 2.58–2.07 (m, 14H), 2.02 (d, J = 9.4 Hz, 1H), 1.88–1.85 (m, 1H), 1.80–1.71 (m, 2H), 1.47–1.46 (m, 1H), 1.44 (t, J = 7.0 Hz, 3H), 1.30–1.18 (m, 16H), 1.02–1.01 (m, 3H), 0.83 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.92, 158.92, 147.72, 126.80, 122.73, 119.38, 114.68, 102.84, 96.01, 79.91, 79.54, 78.62, 77.84, 72.53, 70.81, 68.23, 67.68, 65.34, 65.04, 63.34, 62.81, 58.88, 51.44, 49.93, 49.21, 45.01, 43.96, 41.09, 40.31, 36.67, 34.74, 32.33, 29.46, 22.00, 21.29, 20.94, 18.06, 14.58, 14.50, 10.48; MS (ESI) *m/z* calcd for $C_{47}H_{81}N_5O_{12}$ $[M + 2H]^{2+}/2$: 453.8, found: 454.1.

5.1.2.15. 13(R)-[1-(4-p-Ethoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(20j)***. White solid, yield 24%, mp: 95–98 °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): 7.78–7.64 (m, 3H), 6.94 (d, J = 8.8 Hz, 2H), 5.20 (s, 1H), 4.84 (s, 1H), 4.66–4.56 (m, 2H), 4.45 (d, J = 7.1 Hz, 1H), 4.09–4.02 (m, 3H), 3.84 (s, 1H), 3.59–3.47 (m, 2H), 3.34–3.13 (m, 8H), 3.02–2.96 (m, 2H), 2.90–2.86 (m, 1H), 2.81–2.21 (m, 14H), 2.20–2.00 (m, 3H), 1.96–1.92 (m, 1H), 1.85–1.72 (m, 2H), 1.53 (d, J = 4.2 Hz, 1H), 1.43 (t, J = 7.0 Hz, 3H), 1.38–1.17 (m, 16H), 1.14 (d, J = 6.5 Hz, 3H), 1.01–1.00 (m, 3H), 0.96–0.95 (m, 3H); MS (ESI) *m/z* calcd for $C_{47}H_{81}N_5O_{12}$ $[M + 2H]^{2+}/2$: 453.8, found: 454.1.

5.1.2.16. 13(S)-[1-(4-p-Propoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(20k)***. White solid, yield 39%, mp: 104–106 °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): 7.73 (d, J = 8.7 Hz, 2H), 7.68 (s, 1H), 6.96 (d, J = 8.7 Hz, 2H), 5.53 (d, J = 10.0 Hz, 1H), 4.79–4.78 (m, 1H), 4.57–4.45 (m, 3H), 4.26 (s, 1H), 3.96 (t, J = 6.6 Hz, 3H), 3.72 (d, J = 6.6 Hz, 1H), 3.53–3.52 (m, 2H), 3.27–3.21 (m, 8H), 3.01–2.99 (m, 2H), 2.92–2.89 (m, 1H), 2.78 (s, 3H), 2.74–2.72 (m, 1H), 2.55–2.21 (m, 10H), 2.17–2.05 (m, 3H), 1.85–1.76 (m, 5H), 1.47–1.46 (m, 1H), 1.28–1.23 (m, 16H), 1.19 (d, J = 7.5 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.90, 159.12, 147.73, 126.78, 122.63, 119.39, 114.69, 102.64, 96.00, 79.85, 79.70, 78.59, 77.80, 72.55, 70.72, 69.41, 68.07, 67.64, 65.37, 65.05, 62.84, 58.83, 51.41, 49.94, 49.21, 44.95, 43.92, 41.04, 40.37, 36.70, 34.71, 32.30, 31.24, 22.35, 22.03, 21.29, 20.87, 18.05, 14.54, 10.50, 10.27; MS (ESI) *m/z* calcd for $C_{48}H_{83}N_5O_{12}$ $[M + 2H]^{2+}/2$: 460.8, found: 460.9.

5.1.2.17. 13(R)-[1-(4-p-Propoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(20l)***. White solid, yield 39%, mp: 88–90 °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): 7.74–7.63 (m, 3H), 6.95 (dd, J = 8.9, 2.5 Hz, 2H), 5.15 (s, 1H), 4.81 (s, 1H), 4.68–4.57 (m, 2H), 4.42 (d, J = 7.2 Hz, 1H), 4.06–4.00 (m, 1H), 3.95 (t, J = 6.6 Hz, 2H), 3.83–3.76 (m, 1H), 3.60–3.43 (m, 2H), 3.35–3.18 (m, 8H), 2.99–2.90 (m, 3H), 2.62–2.16 (m, 16H), 2.11–2.10 (m, 1H), 1.94–1.91 (m, 1H), 1.88–1.81 (m, 4H), 1.52–1.49 (m, 1H), 1.32–1.21 (m, 16H), 1.16–1.12 (m, 3H), 1.05 (t, J = 7.4 Hz, 6H), 0.99–0.97 (m, 3H); MS (ESI) *m/z* calcd for $C_{48}H_{83}N_5O_{12}$ $[M + 2H]^{2+}/2$: 460.8, found: 461.2.

5.1.3. Synthesis of C12-substituted 15-membered homoclarithromycin derivatives (Series C)

5.1.3.1. (S)-Methyl 3-azido-2-[(tert-butoxycarbonyl)amino]propanoate ***(37)***. MsC l (10 mL 1 M solution in DCM 10 mmol) was added dropwise to a solution of *N*-Boc-L-serine methyl ester **35** (2 g 9.1 mmol) and Et_3N (1.1 g 10.9 mmol) in dry DCM (50 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 0.5 h and then H_2O (50 mL) was added. The organic phase was separated and aqueous layer

was extracted with DCM (50 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and evaporated *in vacuo* to form the methanesulfonate **36** as a colorless oil. NaN_3 (1.4 g 21.5 mmol) was added to a solution of methanesulfonate **36** in DMF (60 mL) at room temperature. The reaction mixture was stirred at 50 °C for 0.5 h and then H_2O (60 mL) and EtOAc (60 mL) was added. The organic phase was separated and aqueous layer was extracted with EtOAc (60 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and evaporated *in vacuo* to provide the azide **37** (8.74 g) as a colorless oil. The crude intermediate **37** was used directly for the next step without purification.

*5.1.3.2. (S)-Methyl 2-[(tert-butoxycarbonyl)amino]-3-[4-(p-tolyl)-1H-1,2,3-triazol-1-yl]propanoate (**38**).* **37** (8.74 g) in 75% methanol solution (20 mL) was reacted with 4-ethynyltoluene **23** (0.48 g, 4.14 mmol) in the presence of $CuSO_4$ (82 mg) and L-ascorbic acid sodium salt (246 mg) at 35 ~ 40 °C for 48 h. The reaction mixture was evaporated *in vacuo* and the residue was separated chromatographically (PE/EtOAc = 4:1 ~ 1:1) to form the 1,2,3-triazole **38** (0.92 g, 62%) as a white solid. Mp: 146–149 °C, TLC R_f = 0.58 (DCM/MeOH = 30:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.70 (d, *J* = 8.3 Hz, 3H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.41 (d, *J* = 6.4 Hz, 1H), 4.91 (dd, *J* = 13.9, 3.9 Hz, 1H), 4.83 (dd, *J* = 14.0, 4.4 Hz, 1H), 4.76–4.75 (m, 1H), 3.80 (s, 3H), 2.38 (s, 3H), 1.44 (s, 9H); MS (ESI) *m/z* calcd for $C_{18}H_{25}N_4O_4$ $[M + H]^+$: 361.2, found: 361.4.

*5.1.3.3. (S)-2-Amino-3-[4-(p-tolyl)-1H-1,2,3-triazol-1-yl]propan-1-ol (**30a**).* $NaBH_4$ (284 mg, 7.5 mmol) was added to a solution of 1,2,3-triazole **38** (0.9 g, 2.5 mmol) in MeOH (20 mL) at 0 °C. The reaction solution was stirred at 0 °C for 2 h under nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*, and then 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 dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to obtain the primary alcohol **39** as a white solid.

The concentrated HCl (4 mL, 48 mmol) was added to a solution of primary alcohol **39** in EtOAc (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h, and then MeOH (4 mL) and $NaHCO_3$ (5 g, 59.5 mmol) was added. The resulting mixture was stirred at room temperature for 0.5 h and was evaporated *in vacuo* to dryness. The residue was separated chromatographically (DCM/$CH_3OH/NH_3{\cdot}H_2O$ = 10:1:0.1) to form the substituted ethanolamine **30a** (0.35 g, 60% in two steps from intermediate **38**) as a white solid. Mp: 135–138 °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): 8.46 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 4.44 (dd, *J* = 13.6, 4.9 Hz, 1H), 4.18 (dd, *J* = 13.6, 7.8 Hz, 1H), 3.32–3.29 (m, 2H), 3.13–3.09 (m, 1H), 2.33 (s, 3H), 1.90 (s, 1H); MS (ESI) *m/z* calcd for $C_{12}H_{17}N_4O$ $[M + H]^+$: 233.1, found: 233.3.

*5.1.3.4. Ring-opening intermediate with carboxylic acid (**32a**).* To a solution of **3** (400 mg, 0.37 mmol) in anhydrous $CHCl_3$ (20 mL) was added $Pb(OAc)_4$ (195 mg, 0.44 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h under nitrogen atmosphere. The aldehyde **4** was obtained in a high yield and was directly used in the next step without purification.

To a solution of **4** were added **30a** (170 mg, 0.73 mmol) and NaBH$(OAc)_3$ (233 mg, 1.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h under nitrogen atmosphere. Then, NaBH$(OAc)_3$ (233 mg, 1.1 mmol) and 37% aqueous formaldehyde solution (179 mg, 2.2 mmol) were added and stirred at room temperature for another 4 h under nitrogen atmosphere. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (DCM/$CH_3OH/NH_3{\cdot}H_2O$ = 30:1:0.1) to yield the crude ester **31a** as a colorless oil.

LiOH (44 mg, 1.83 mmol) was added to a solution of the above **31a** in the mixed solvents of THF (15 mL), EtOH (5 mL) and H_2O (5 mL) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was evaporated *in vacuo* to dryness and the residue was separated chromatographically (DCM/$CH_3OH/NH_3{\cdot}H_2O$ = 15:1:0.1 ~ 10:1:0.1) to give the carboxylic acid **32a** (70 mg, 15% in four steps from intermediate **3**) as a white solid. Mp: 83–86 °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): 7.80 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.75 (s, 1H), 4.68–4.60 (m, 1H), 4.55–4.49 (m, 1H), 4.44–4.35 (m, 1H), 4.29–4.26 (m, 1H), 4.04–3.89 (m, 2H), 3.84–3.76 (m, 1H), 3.60–3.56 (m, 1H), 3.37 (s, 1H), 3.31 (s, 3H), 3.24–3.10 (m, 5H), 2.87–2.58 (m, 5H), 2.44 (s, 3H), 2.38 (s, 3H), 2.33–2.11 (m, 8H), 2.07–1.99 (m, 1H), 1.93–1.86 (m, 1H), 1.77–1.72 (m, 1H), 1.71–1.52 (m, 2H), 1.49 (dd, *J* = 14.9, 4.9 Hz, 1H), 1.26 (s, 3H), 1.24–1.20 (m, 4H), 1.18–1.05 (m, 13H), 0.98–0.86 (m, 33H), 0.69–0.55 (m, 18H); MS (ESI) *m/z* calcd for $C_{64}H_{123}N_5O_{12}Si_3$ $[M + 2H]^{2+}$/2: 618.9, found: 619.5.

*5.1.3.5. 15-Membered 11a-homo-aza-clarithromycin intermediate (**33a**).* To a suspension of **32a** (70 mg, 0.06 mmol) and Et_3N (58 mg, 0.57 mmol) in THF (5 mL) was added 2,4,6-trichlorobenzoyl chloride (42 mg, 0.17 mmol) at room temperature. The reaction solution was stirred at room temperature for 4 h under nitrogen atmosphere, and was added to a refluxed solution of DMAP (175 mg, 1.42 mmol) in CH_3CN (30 mL) for 0.5 h. The reaction mixture was concentrated *in vacuo* to dryness, and then DCM (20 mL) and saturated NH_4Cl solution (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 anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (PE/acetone = 15:1 ~ 10:1) to afford the cyclic intermediate **33a** (50 mg, 72%) as a white solid. Mp: 81–84 °C, TLC R_f = 0.53 (PE/acetone = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.77–7.67 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 2H), 4.71 (s, 1H), 4.47–4.38 (m, 3H), 4.30–4.25 (m, 1H), 4.21–4.14 (m, 1H), 4.10–4.04 (m, 1H), 3.67 (s, 1H), 3.57–3.54 (m, 1H), 3.52–3.49 (m, 1H), 3.28 (s, 3H), 3.21–3.17 (m, 5H), 2.71–2.60 (m, 2H), 2.53–2.24 (m, 11H), 2.24–2.19 (m, 6H), 2.06–2.01 (m, 1H), 1.78–1.72 (s, 2H), 1.61–1.55 (m, 2H), 1.44–1.40 (m, 1H), 1.26 (s, 3H), 1.24–1.22 (m, 1H), 1.22–1.20 (m, 3H), 1.18–1.12 (m, 10H), 1.09–1.08 (m, 3H), 1.00–0.92 (m, 33H), 0.68–0.55 (m, 18H); MS (ESI) *m/z* calcd for $C_{64}H_{121}N_5O_{11}Si_3$ $[M + 2H]^{2+}$/2: 609.9, found: 610.4.

*5.1.3.6. 12(S)-[1-(4-p-Methylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34a**).* To a solution of **33a** (50 mg, 0.04 mmol) in THF (5 mL) was added hydrogen fluoride–pyridine (19 mg, 0.12 mmol, 65%) at room temperature, and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (20 mL) and diluted with DCM (20 mL). The organic phase was separated and aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was separated chromatographically (DCM/$CH_3OH/NH_3{\cdot}H_2O$ = 10:1:0.1) to obtain compound **34a** (15 mg, 42%) as a white solid. Mp: 91–94 °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): 7.85 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.75–4.74 (m, 1H), 4.57 (dd, *J* = 14.2, 6.6 Hz, 1H), 4.52 (d, *J* = 7.2 Hz, 1H), 4.41 (dd, *J* = 14.0, 7.4 Hz, 1H), 4.28 (d, *J* = 11.9 Hz, 1H), 4.17 (s, 1H), 4.05–3.99 (m, 2H), 3.84 (d, *J* = 4.3 Hz, 1H), 3.49–3.48 (m, 2H), 3.27 (s, 3H), 3.18–3.15 (m, 4H), 3.03 (d, *J* = 8.8 Hz, 1H), 2.95–2.88 (m, 2H), 2.46–2.38 (m, 11H), 2.32–2.21 (m, 6H), 2.06–1.95 (m, 5H), 1.78–1.76 (m, 1H), 1.58 (dd, *J* = 14.8, 4.9 Hz, 1H), 1.26–1.25 (m, 13H), 1.17 (d, *J* = 1.9 Hz, 3H), 1.02 (d, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.1 Hz, 3H), 0.76 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ

ppm): 175.60, 148.13, 138.23, 129.59, 127.51, 125.63, 120.10, 80.60, 77.46, 72.90, 71.66, 70.59, 68.30, 68.10, 68.05, 65.62, 63.64, 49.43, 46.08, 43.87, 35.94, 34.68, 31.91, 30.31, 29.78, 29.70, 29.61, 29.52, 29.32, 29.24, 27.22, 25.54, 22.69, 21.69, 21.30, 20.90, 20.79, 18.87, 18.42, 14.12; HRMS (ESI) *m/z* calcd for $C_{46}H_{78}N_5O_{11}$ $[M + H]^+$: 876.5698, $[M + 2H]^{2+}/2$: 438.7888, found: 876.5682, 438.7885.

According to the synthetic procedure of compound **34a**, the other compounds (**34b-34l**) in Series C were also prepared.

*5.1.3.7. 12(R)-[1-(4-p-Methylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34b**).* White solid, yield 83%, mp: 99–102 °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): 7.78 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.85 (d, *J* = 3.8 Hz, 1H), 4.69 (s, 1H), 4.52 (d, *J* = 7.0 Hz, 1H), 4.40 (s, 2H), 4.06 (d, *J* = 7.3 Hz, 1H), 4.01–3.96 (m, 1H), 3.75 (d, *J* = 7.3 Hz, 2H), 3.61–3.53 (m, 2H), 3.30–3.25 (m, 7H), 3.06–3.03 (m, 3H), 2.90–2.86 (m, 2H), 2.86–2.82 (m, 3H), 2.57 (s, 1H), 2.48 (s, 3H), 2.38 (s, 3H), 2.34–2.16 (m, 5H), 1.92–1.84 (m, 2H), 1.66–1.51 (m, 7H), 1.30–1.26 (m, 13H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.83–0.81 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 175.73, 147.67, 138.24, 129.58, 127.56, 125.60, 120.38, 102.19, 96.41, 80.23, 80.15, 78.59, 77.80, 72.90, 71.04, 68.30, 68.11, 67.98, 65.99, 65.26, 62.69, 61.56, 50.58, 49.39, 44.59, 35.13, 29.71, 29.33, 21.56, 21.31, 20.99, 18.87, 18.32, 14.80, 10.62; HRMS (ESI) *m/z* calcd for $C_{46}H_{78}N_5O_{11}$ $[M + H]^+$: 876.5698, $[M + 2H]^{2+}/2$: 438.7888, found: 876.5658, 438.7889.

*5.1.3.8. 12(S)-[1-(4-p-Ethylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34c**).* White solid, yield 24%, mp: 92–94 °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 (s, 1H), 7.74–7.73 (m, 3H), 7.25 (s, 1H), 4.77 (d, *J* = 4.1 Hz, 1H), 4.53 (dd, *J* = 13.6, 6.7 Hz, 1H), 4.48 (d, *J* = 7.1 Hz, 1H), 4.39 (dd, *J* = 13.9, 7.4 Hz, 2H), 4.22 (d, *J* = 11.7 Hz, 1H), 4.15 (s, 1H), 4.05–3.96 (m, 3H), 3.80 (d, *J* = 5.1 Hz, 1H), 3.49–3.48 (m, 2H), 3.29–3.25 (m, 4H), 3.16 (s, 3H), 3.00–2.99 (m, 1H), 2.97–2.89 (m, 2H), 2.70–2.66 (m, 2H), 2.48–2.27 (m, 14H), 2.02–1.99 (m, 3H), 1.81–1.71 (m, 3H), 1.58–1.53 (m, 1H), 1.30 (s, 3H), 1.27–1.23 (m, 13H), 1.17 (d, *J* = 7.3 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.81–0.80 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 175.44, 147.96, 144.34, 128.25, 127.84, 125.63, 119.94, 103.01, 95.70, 95.51, 80.61, 78.64, 78.46, 77.92, 77.81, 72.72, 70.79, 68.64, 65.77, 65.41, 61.84, 50.15, 49.34, 49.23, 47.73, 44.05, 40.33, 34.92, 34.61, 34.16, 28.58, 21.54, 21.51, 21.15, 21.11, 20.76, 18.13, 18.07, 15.40, 13.02, 10.96; MS (ESI) *m/z* calcd for $C_{47}H_{81}N_5O_{11}$ $[M + 2H]^{2+}/2$: 445.8, found: 446.1.

*5.1.3.9. 12(R)-[1-(4-p-Ethylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34d**).* White solid, yield 52%, mp: 92–95 °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): 7.79 (s, 1H), 7.72–7.70 (m, 3H), 7.25 (s, 1H), 4.87 (d, *J* = 4.2 Hz, 1H), 4.61 (s, 1H), 4.50 (d, *J* = 7.0 Hz, 1H), 4.45–4.36 (m, 3H), 4.07–4.00 (m, 3H), 3.75 (d, *J* = 7.5 Hz, 1H), 3.44–3.38 (m, 2H), 3.30–3.25 (m, 7H), 3.05–3.02 (m, 1H), 2.91–2.86 (m, 2H), 2.70–2.66 (m, 2H), 2.48–2.16 (m, 14H), 2.06–1.91 (m, 3H), 1.87–1.77 (m, 3H), 1.56 (d, *J* = 4.7 Hz, 1H), 1.32 (s, 3H), 1.27–1.23 (m, 13H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.87–0.83 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 175.79, 147.68, 144.43, 128.26, 127.77, 125.62, 120.18, 102.45, 96.08, 80.22, 79.88, 78.70, 77.81, 72.76, 70.96, 68.19, 68.01, 65.77, 65.20, 62.53, 61.68, 50.47, 49.30, 44.55, 40.55, 36.29, 35.01, 32.04, 29.59, 28.57, 21.46, 21.07, 18.76, 18.23, 15.39, 14.46, 10.32; MS (ESI) *m/z* calcd for $C_{47}H_{81}N_5O_{11}$ $[M + 2H]^{2+}/2$: 445.8, found: 446.1.

*5.1.3.10. 12(S)-[1-(4-p-n-Propylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34e**).* White solid, yield 34%, mp: 84–87 °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): 7.86 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.74 (s, 1H), 4.58 (dd, *J* = 14.0, 6.5 Hz, 1H), 4.52 (d, *J* = 7.2 Hz, 1H), 4.41 (dd, *J* = 14.1, 7.3 Hz, 2H), 4.28 (d, *J* = 10.4 Hz, 1H), 4.20 (s, 1H), 4.03–3.94 (m, 3H), 3.85 (d, *J* = 3.8 Hz, 1H), 3.51–3.48 (m, 2H), 3.28–3.24 (m, 4H), 3.15 (s, 3H), 3.04–3.03 (m, 1H), 2.98–2.93 (m, 2H), 2.63–2.60 (m, 2H), 2.45–2.17 (m, 14H), 2.05–1.99 (m, 3H), 1.96–1.95 (m, 1H), 1.79–1.76 (m, 2H), 1.67–1.65 (m, 2H), 1.58–1.57 (m, 1H), 1.28 (s, 3H), 1.25–1.24 (m, 10H), 1.16 (d, *J* = 7.3 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.96–0.95 (m, 3H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.76–0.75 (m, 3H); MS (ESI) *m/z* calcd for $C_{48}H_{83}N_5O_{11}$ $[M + 2H]^{2+}/2$: 452.8, found: 453.2.

*5.1.3.11. 12(R)-[1-(4-p-n-Propylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34f**).* White solid, yield 77%, mp: 106–108 °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): 7.78 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.86 (d, *J* = 4.3 Hz, 1H), 4.60 (s, 1H), 4.50 (d, *J* = 7.0 Hz, 1H), 4.41–4.36 (m, 2H), 4.07–3.99 (m, 2H), 3.75 (d, *J* = 7.3 Hz, 1H), 3.47–3.39 (m, 2H), 3.30–3.25 (m, 7H), 3.05–3.02 (m, 1H), 2.92–2.86 (m, 2H), 2.63–2.60 (m, 2H), 2.48–2.21 (m, 11H), 2.08–1.91 (m, 3H), 1.73–1.56 (m, 9H), 1.32 (s, 3H), 1.30–1.25 (m, 10H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 7.4 Hz, 3H), 0.87–0.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.66, 147.56, 142.70, 128.72, 127.65, 125.39, 120.05, 102.34, 95.92, 80.09, 79.75, 78.58, 77.69, 72.63, 70.81, 68.04, 65.61, 65.07, 62.38, 61.58, 50.31, 49.16, 44.43, 40.45, 40.30, 37.57, 36.18, 34.88, 31.89, 30.81, 29.44, 24.19, 21.31, 20.94, 18.09, 14.29, 13.51, 10.15; MS (ESI) *m/z* calcd for $C_{48}H_{83}N_5O_{11}$ $[M + 2H]^{2+}/2$: 452.8, found: 453.1.

*5.1.3.12. 12(S)-[1-(4-p-n-Amylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34g**).* White solid, yield 30%, mp: 96–98 °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 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.77–4.76 (m, 1H), 4.54 (dd, *J* = 12.1, 7.0 Hz, 1H), 4.48 (d, *J* = 7.0 Hz, 1H), 4.39 (dd, *J* = 14.0, 7.4 Hz, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.16 (s, 1H), 4.08–3.94 (m, 3H), 3.81 (s, 1H), 3.50–3.45 (m, 2H), 3.28 (s, 3H), 3.21–3.16 (m, 4H), 3.02–3.00 (m, 1H), 2.96–2.89 (m, 2H), 2.64–2.61 (m, 2H), 2.48–2.21 (m, 12H), 2.06–1.98 (m, 3H), 1.81–1.75 (m, 2H), 1.68–1.61 (m, 6H), 1.34–1.32 (m, 4H), 1.29 (s, 3H), 1.27–1.21 (m, 10H), 1.17 (d, *J* = 7.3 Hz, 3H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.93–0.88 (m, 6H), 0.83–0.80 (m, 3H); MS (ESI) *m/z* calcd for $C_{50}H_{87}N_5O_{11}$ $[M + 2H]^{2+}/2$: 466.8, found: 467.2.

*5.1.3.13. 12(R)-[1-(4-p-n-Amylphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34h**).* White solid, yield 74%, mp: 102–104 °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): 7.78 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.87 (d, *J* = 4.4 Hz, 1H), 4.60–4.54 (m, 1H), 4.49 (d, *J* = 7.1 Hz, 1H), 4.45–4.41 (m, 1H), 4.36–4.32 (m, 1H), 4.06–4.01 (m, 2H), 3.81 (d, *J* = 7.7 Hz, 1H), 3.75 (d, *J* = 7.4 Hz, 2H), 3.58–3.49 (m, 2H), 3.31–3.25 (m, 7H), 3.04 (s, 1H), 2.90–2.88 (m, 2H), 2.64–2.61 (m, 2H), 2.48–2.25 (m, 12H), 2.07 (s, 2H), 1.96–1.80 (m, 4H), 1.68–1.55 (m, 5H), 1.33–1.24 (m, 17H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.91–0.84 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.73, 147.52, 142.90, 128.61, 127.55, 125.35, 120.01, 102.37, 95.82, 80.06, 79.71, 78.57, 77.68, 72.57, 70.77, 67.94, 65.50, 64.83, 62.29, 61.60, 50.27, 49.11, 44.40, 40.52, 40.02, 36.11, 35.41, 34.81, 31.16, 30.75, 30.53, 22.22, 21.25, 20.92, 18.07, 14.23, 13.72, 10.03; MS (ESI) *m/z* calcd for $C_{50}H_{87}N_5O_{11}$ $[M + 2H]^{2+}/2$: 466.8, found: 467.1.

*5.1.3.14. 12(S)-[1-(4-p-Ethoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin (**34i**).* White solid, yield 35%, mp: 106–108 °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): 7.78 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.76–4.75 (m, 1H), 4.57–4.53 (m, 1H), 4.50 (d,

J = 7.2 Hz, 1H), 4.41–4.37 (m, 1H), 4.26 (d, J = 11.3 Hz, 1H), 4.17 (s, 1H), 4.07 (d, J = 7.0 Hz, 2H), 4.03–3.94 (m, 4H), 3.83 (d, J = 4.8 Hz, 1H), 3.49–3.47 (m, 2H), 3.27–3.25 (m, 4H), 3.15 (s, 3H), 3.03–3.01 (m, 1H), 2.95–2.89 (m, 2H), 2.49–2.21 (m, 14H), 2.01–1.94 (m, 3H), 1.80–1.75 (m, 3H), 1.58 (d, J = 5.0 Hz, 1H), 1.43 (t, J = 7.0 Hz, 3H), 1.27–1.24 (m, 13H), 1.17 (d, J = 7.3 Hz, 3H), 1.03 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H); MS (ESI) *m/z* calcd for $C_{47}H_{81}N_5O_{12}$ $[M + 2H]^{2+}/2$: 453.8, found: 454.1.

5.1.3.15. 12(R)-[1-(4-p-Ethoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(34j)***. White solid, yield 63%, mp: 102–104 °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): 7.74–7.69 (m, 3H), 6.94 (d, J = 7.0 Hz, 2H), 4.86 (d, J = 4.2 Hz, 1H), 4.61 (s, 1H), 4.50 (d, J = 7.1 Hz, 1H), 4.38 (d, J = 28.9 Hz, 2H), 4.09–3.99 (m, 4H), 3.79–3.75 (m, 2H), 3.50–3.39 (m, 2H), 3.33–3.17 (m, 7H), 3.04–3.03 (m, 1H), 2.89–2.82 (m, 2H), 2.82–2.58 (m, 5H), 2.48 (s, 3H), 2.39–2.18 (m, 5H), 2.04–1.89 (m, 2H), 1.86–1.67 (m, 5H), 1.56 (d, J = 4.7 Hz, 1H), 1.44 (t, J = 7.0 Hz, 3H), 1.32–1.24 (m, 13H), 1.18 (d, J = 7.1 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 0.86–0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 175.65, 158.83, 147.34, 126.75, 122.73, 119.60, 114.62, 102.14, 95.94, 80.00, 79.86, 78.47, 77.64, 72.64, 70.71, 67.82, 65.62, 65.05, 63.30, 62.35, 61.51, 50.28, 49.13, 44.40, 36.19, 34.86, 32.01, 31.43, 21.28, 21.00, 20.84, 18.07, 14.54, 14.34, 10.18; MS (ESI) *m/z* calcd for $C_{47}H_{81}N_5O_{12}$ $[M + 2H]^{2+}/2$: 453.8, found: 453.7.

5.1.3.16. 12(S)-[1-(4-p-Propoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(34k)***. White solid, yield 47%, mp: 88–91 °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): 7.78–7.72 (m, 3H), 6.96 (d, J = 8.8 Hz, 2H), 4.75 (s, 1H), 4.59–4.47 (m, 3H), 4.39 (dd, J = 14.1, 7.5 Hz, 1H), 4.31–4.27 (m, 1H), 4.23–4.16 (m, 1H), 4.03–4.00 (m, 1H), 3.96 (t, J = 6.6 Hz, 2H), 3.84 (d, J = 4.4 Hz, 1H), 3.49–3.47 (m, 2H), 3.26–3.14 (m, 7H), 3.03 (s, 1H), 2.97–2.91 (m, 2H), 2.85–2.65 (m, 6H), 2.49–2.14 (m, 11H), 2.03–1.92 (m, 3H), 1.85–1.77 (m, 3H), 1.28–1.24 (m, 13H), 1.17 (d, J = 7.3 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 5.9 Hz, 3H), 0.77–0.76 (m, 3H); MS (ESI) *m/z* calcd for $C_{48}H_{83}N_5O_{12}$ $[M + 2H]^{2+}/2$: 460.8, found: 461.1.

5.1.3.17. 12(R)-[1-(4-p-Propoxyphenyl-1H-1,2,3-triazol-1-yl)-1-methylene]-9(S)-hydroxyclarithromycin ***(34l)***. White solid, yield 57%, mp: 84–86 °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): 7.73–7.68 (m, 3H), 6.94 (d, J = 8.8 Hz, 2H), 4.85 (d, J = 3.8 Hz, 1H), 4.68 (s, 1H), 4.52 (d, J = 7.0 Hz, 1H), 4.39 (s, 2H), 4.06–4.05 (m, 1H), 4.01–3.94 (m, 4H), 3.74 (s, 1H), 3.62–3.55 (m, 2H), 3.30–3.28 (m, 4H), 3.24 (s, 3H), 3.12–3.01 (m, 4H), 2.94–2.83 (m, 6H), 2.60–2.13 (m, 10H), 1.92 (s, 1H), 1.85–1.81 (m, 2H), 1.58 (dd, J = 15.0, 4.7 Hz, 3H), 1.30–1.26 (m, 13H), 1.19 (d, J = 8.1 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.83–0.81 (m, 6H); MS (ESI) *m/z* calcd for $C_{48}H_{83}N_5O_{12}$ $[M + 2H]^{2+}/2$: 460.8, found: 461.2.

5.2. Bactericidal or bacteriostatic assay

The MIC values of Series A, B and C against sensitive bacterial strains (*S. aureus* ATCC25923, *E. coli* ATCC25922, *P. aeruginosa* ATCC27853 and *B. subtilis* ATCC9372) and resistant bacterial strains (*S. aureus* ATCC31007, *S. aureus* ATCC43300, *S. pneumonia* B1, *S. pneumoniae* AB11 and *S. pyogenes* 1) were determined using CAM and AZM as reference compounds. The MIC values of compounds were determined by the broth microdilution method. The prepared compounds and the two reference compounds were added to in cation adjusted Mueller-Hinton (CAMH) in a 96-well plate and well mixed. Then, the concentration of each compound in a 96-well plate was range from 0.25 to 128 μg/mL or from 0.5 to 256 μg/mL by using 2-fold dilution method. Bacteria are inoculated into the above prepared solution of each well and incubated for 24 h at 37 °C. The turbidity of each well was observed, and the MIC was determined as the concentration at which no visible bacterial proliferation was seen. The solution (10 μL), from wells where no visible bacterial proliferation was seen (in the MIC 96-well plates), onto culture medium plates. The plates were subcultured for 24 h at 37 °C. The MBC was determined as the lowest concentration at which no bacterial colonies were seen.

5.3. Docking methods

The crystal structure of the *E. coli* ribosome bound to the peptidyl transferase center was obtained from the Protein Data Bank (code: 4V7S). Compounds $\mathbf{9e_{pre}}$, **11g** and **20c** were docked by Ledock, and CAM was used as the control compound. The alkyl group of compounds **11g** were docked into binding site, which may bind to bacterial ribosome by the π-π stacking, electrostatic and hydrophobic interaction. The binding conformation was given by using the conformation search function of simulated annealing-genetic algorithm.

5.4. Time-bactericidal assay

S. pneumoniae AB11 cells in log-phase were diluted to approximate 10^6 CFU/mL and exposed to a series of concentrations of compound **11g** (0.5 × MIC, 1 × MIC, 2 × MIC and 4 × MIC, MIC = 4 μg/mL) in CAMH broth. The solution were obtained from each treatment after 0, 3, 6, 9, 12 and 24 h of incubation at 37 °C. The solution was serially diluted in CAMH broth by using 10-fold dilution method. Therefore, 10 concentrations of bacterial solution were obtained and were plated onto TSA plates. This plates were incubated for 24 h at 37 °C prior to viable CFU/mL was provided.

5.5. Cytotoxicity assay

A 28 h continuous MTT method was used to evaluate the toxicity of compounds **20c**, **20d** and **20f** to MCF-7 breast cancer cells. After the MCF-7 breast cancer cells (approximately 10^4 cells/well) were cultured in 96-well plates for 24 h, the drug solution of **20c**, **20d** and **20f** was added. After the above mixtures were cultured for 24 h, the solution of MTT was added, and then continued to be cultured for 4 h at 37 °C. The liquid in the mixture was carefully absorbed and discarded, and then DMSO was added. The absorbance of each well was obtained at 570 nm on an enzyme-labeled instrument.

Declaration of Competing Interest

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

Acknowledgements

This work was supported financially by National Natural Science Foundation of China (81973179 and 81673284) and Key Project of Major Project of New and Old Kinetic Energy Conversion in 2020.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2021.104992.

References

[1] G.M. Reddy, G. Sravya, G. Yuvaraja, A. Camilo, G.V. Zyryanov, J.R. Garcia, Highly functionalized pyranopyrazoles: synthesis, antimicrobial activity, simulation studies and their structure activity relationships (SARs), Res. Chem. Intermediate. 44 (2018) 7491–7507.

[2] G.M. Reddy, J.R. Garcia, G.V. Zyryanov, G. Sravya, N.B. Reddy, Pyranopyrazoles as efficient antimicrobial agents: green, one pot and multicomponent approach, Bioorg. Chem. 82 (2019) 324–331.
[3] G.M. Reddy, J.R. Garcia, G. Yuvaraja, M. Venkata Subbaiah, J.C. Wen, Design, synthesis of tri-substituted pyrazole derivatives as promising antimicrobial agents and investigation of structure activity relationships, J. Heterocycl. Chem., 57 (2020) 2288-2296.
[4] G.M. Reddy, A. Camilo, Biologically active dihydropyridines: An efficient green synthesis, antimicrobial properties, machine aided results and SARs, Sustain. Chem. Pharm. 17 (2020), 100303.
[5] B.R. Nemallapudi, G.V. Zyryanov, B. Avula, M.R. Guda, S. Gundala, An effective green and ecofriendly catalyst for synthesis of bis (indolyl) methanes as promising antimicrobial agents, J. Heterocycl. Chem. 56 (2019) 3324–3332.
[6] S. Pal, A journey across the sequential development of macrolides and ketolides related to erythromycin, Tetrahedron 62 (2006) 3171–3200.
[7] J.M. McGuire, Ilotycin, a new antibiotic, Antibiot. Chemother. 2 (1952) 281–283.
[8] P. Kurath, P.H. Jones, R.S. Egan, T.J. Perun, Acid degradation of erythromycin A and erythromycin B, Experientia 27 (1971) 362.
[9] S. Omura, S. Morimoto, T. Nagate, T. Adachi, Y. Kohno, Research and development of clarithromycin, Yakugaku Zasshi 112 (1992) 593–614.
[10] J. Retsema, A. Girard, W. Schelkly, M. Manousos, M. Anderson, G. Bright, R. Borovoy, L. Brennan, R. Mason, Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms, Antimicrob. Agents. Chemother. 31 (1987) 1939–1947.
[11] A.E. Girard, D. Girard, A.R. English, T.D. Gootz, C.R. Cimochowski, J.A. Faiella, S. L. Haskell, J.A. Retsema, Pharmacokinetic and in vivo studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution, Antimicrob. Agents. Chemother. 31 (1987) 1948–1954.
[12] S. Schonwald, V. Skerk, I. Petricevic, V. Car, L. Majerus-Misic, M. Gunjaca, Comparison of three-day and five-day courses of azithromycin in the treatment of atypical pneumonia, Eur. J. Clin. Microbiol. Infect. Dis. 10 (1991) 877–880.
[13] T. Asaka, A. Manaka, H. Sugiyama, Recent developments in macrolide antimicrobial research, Curr. Top. Med. Chem. 3 (2003) 961–989.
[14] R.F. Keyes, J.J. Carter, E.E. Englund, M.M. Daly, G.G. Stone, A.M. Nilius, Z. Ma, Synthesis and antibacterial activity of 6-O-arylbutynyl ketolides with improved activity against some key erythromycin-resistant pathogens, J. Med. Chem. 46 (2003) 1795–1798.
[15] M. Nguyen, E.P. Chung, Telithromycin: The first ketolide antimicrobial, Clin. Ther. 27 (2005) 1144–1163.
[16] G.G. Zhanel, E. Hartel, H. Adam, S. Zelenitsky, M.A. Zhanel, A. Golden, F. Schweizer, B. Gorityala, Philippe R. S. Lagace-Wiens, A.J. Walkty, et al, Solithromycin: A Novel Fluoroketolide for the Treatment of Community-Acquired Bacterial Pneumonia, Drugs, 76 (2016) 1737-1757.
[17] A. Denis, C. Agouridas, J.M. Auger, Benedetti Y. Benedetti, A. Bonnefoy, F. Bretin, J.F. Chantot, A. Dussarat, C. Fromentin, S.G. D'Ambrieres, S. Lachaud, P. Laurin, O. Martret, V. Loyau, N. Tessot, Jean-Marie Pejac, S. Perron, Synthesis and antibacterial activity of HMR 3647, a new ketolide highly potent against erythromycin-resistant and susceptible pathogens, Bioorg. Med. Chem. Lett., 9 (1999) 3075-3080.
[18] Y.S. Or, R.F. Clark, S. Wang, D.T. Chu, A.M. Nilius, R.K. Flamm, M. Mitten, P. Ewing, J. Alder, Z.J. Ma, Design, synthesis, and antimicrobial activity of 6-O-substituted ketolides active against resistant respiratory tract pathogens, J. Med. Chem. 43 (2000) 1045–1049.
[19] R. Berisio, J. Harms, F. Schluenzen, R. Zarivach, Harly A.S. Hansen, P. Fucini, A. Yonath, Structural insight into the antibiotic action of telithromycin against resistant mutants, J. Bacteriol. 185 (2003) 4276–4279.
[20] B. Llano-Sotelo, J. Dunkle, D. Klepacki, W. Zhang, P. Fernandes, Jamie H.D. Cate, A.S. Mankin, Binding and action of CEM-101, a new fluoroketolide antibiotic that inhibits protein synthesis, Antimicrob. Agents. Chemother. 54 (2010) 4961–4970.
[21] D. Bulkley, C.A. Innis, G. Blaha, T.A. Steitz, Revisiting the structures of several antibiotics bound to the bacterial ribosome, Proc. Natl. Acad. Sci. USA 107 (2010) 17158–17163.
[22] Z. Eyal, D. Matzov, M. Krupkin, I. Wekselman, E. Zimmerman, H. Rozenberg, A. Bashan, A. Yonath, S. Paukner, Structural insights into species-specific features of the ribosome from the pathogen Staphylococcus aureus, Proc. Natl. Acad. Sci. USA 112 (2015) E5805–E5814.
[23] Z. Ma, R.F. Clark, A. Brazzale, S. Wang, M.J. Rupp, L. Li, G. Griesgraber, S. Zhang, H. Yong, L.T. Phan, P.A. Nemoto, Daniel T.W. Chu, J.J. Plattner, X. Zhang, P. Zhong, Z. Cao, A.M. Nilius, V.D. Shortridge, R. Flamm, M. Mitten, J. Meulbroek, P. Ewing, J. Alder, Y.S. Or, Novel erythromycin derivatives with aryl groups tethered to the C-6 position are potent protein synthesis inhibitors and active against multidrug-resistant respiratory pathogens, J. Med. Chem. 44 (2001) 4137–4156.
[24] A. Janas, P. Przybylski, 14-and 15-membered lactone macrolides and their analogues and hybrids: structure, molecular mechanism of action and biological activity, Eur. J. Med. Chem. 182 (2019), 111662.
[25] A. Janas, P. Pecyna, M. Gajecka, F. Bartl, P. Przybylski, Synthesis and antibacterial activity of new N-alkylammonium and carbonate-triazole derivatives within desosamine of 14- and 15-membered lactone macrolides, ChemMedChem 15 (2020) 1529–1551.
[26] S.J. Shaw, D. Abbanat, G.W. Ashley, K. Bush, B. Foleno, M. Macielag, D. Zhang, D. C. Myles, 15-amido erythromycins: synthesis and in vitro activity of a new class of macrolide antibiotics, J. Antibiot. (Tokyo) 58 (2005) 167–177.
[27] G.W. Ashley, M. Burlingame, R. Desai, H. Fu, T. Leaf, P.J. Licari, C. Tran, D. Abbanat, K. Bush, M. Macielag, Preparation of erythromycin analogs having functional groups at C-15, J. Antibiot. (Tokyo) 59 (2006) 392–401.
[28] T. Miura, K. Kanemoto, S. Natsume, K. Atsumi, H. Fushimi, T. Yoshida, K. Ajito, Novel azalides derived from 16-membered macrolides. Part II: Isolation of the linear 9-formylcarboxylic acid and its sequential macrocyclization with an amino alcohol or an azidoamine, Bioorg. Med. Chem. 16 (2008) 10129–10156.
[29] T. Sugimoto, T. Tanikawa, Synthesis and antibacterial activity of a novel class of 15-membered macrolide antibiotics, "11a-azalides", ACS Med. Chem. Lett. 2 (2011) 234–237.
[30] Y. Qin, Y. Teng, R. Ma, F. Bi, Z. Liu, P. Zhang, S. Ma, Design, synthesis and antibacterial evaluation of novel 15-membered 11a-azahomoclarithromycin derivatives with the 1,2,3-triazole side chain, Eur. J. Med. Chem. 180 (2019) 321–339.
[31] J.A. Dunkle, L. Xiong, A.S. Mankin, J.H.D. Cate, Structures of the Escherichia coli ribosome with antibiotics bound near the peptidyl transferase center explain spectra of drug action, Proc. Natl. Acad. Sci. USA 107 (2010) 17152–17157.
[32] A.S. Mankin, Macrolide myths, Curr. Opin. Microbiol. 11 (2008) 414–421.
[33] F. Schlunzen, R. Zarivach, J. Harms, A. Bashan, A. Tocilj, R. Albrecht, A. Yonath, F. Franceschi, Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria, Nature 413 (2001) 814–821.
[34] W. Chen, Henry N.C. Wong, T.W. Daniel, X. Chu, Lin, Synthetic studies of erythromycin derivatives: 6-O-methylation of (9S)-12, 21-anhydro-9-dihydroery-thromycin A derivatives, Tetrahedron 59 (2003) 7033–7045.
[35] T. Sugimoto, T. Tanikawa, K. Suzuki, Y. Yamasaki, Synthesis and structure-activity relationship of a novel class of 15-membered macrolide antibiotics known as '11a-azalides', Bioorg. Med. Chem. 20 (2012) 5787–5801.
[36] A.F. Abdel-Magid, K.G. Carson, B.D. Harris, C.A. Maryanoff, R.D. Shah, Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures(1), J. Org. Chem. 61 (1996) 3849–3862.
[37] M. Hikota, H. Tone, K. Horita, O. Yonemitsu, Chiral synthesis of polyketide-derived natural products. 27. Stereoselective synthesis of erythronolide A via an extremely efficient macrolactonization by the modified Yamaguchi method, J. Org. Chem. 55 (1990) 7–9.
[38] Y. Wu, M. Pan, Y. Dai, B. Liu, J. Cui, W. Shi, Q. Qiu, W. Huang, H. Qian, Design, synthesis and biological evaluation of LBM-A5 derivatives as potent P-glycoprotein-mediated multidrug resistance inhibitors, Bioorg. Med. Chem. 24 (2016) 2287–2297.
[39] V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, A stepwise huisgen cycloaddition process: copper (I)-catalyzed regioselective "ligation" of azides and terminal alkynes, Angew. Chem. Int. Edit. 41 (2002) 2596–2599.
[40] Y. Shi, Q. Xiao, Q. Lan, D.H. Wang, L.Q. Jia, X.H. Tang, T. Zhou, M. Li, W.S. Tian, A synthesis of cephalostatin 1, Tetrahedron 75 (2019) 1722–1738.
[41] R. Tammana, K.K. Vemula, R. Guruvindapalli, R. Yanamandra, M. Gutta, An expeditious construction of 3-aryl-5-(substituted methyl)-2-oxazolidinones: a short and efficient synthesis of Linezolid, ARKIVOC (Gainesville, FL, U.S.) 6 (2012) 45–56.
[42] T.V. Golobokova, A.G. Proidakov, L.I. Vereshchagin, V.N. Kizhnyaev, Synthesis of N-(oxyran-2-ylmethyl)triazoles and -tetrazoles, Russ. J. of Org. Chem. 51 (2015) 1308–1312.
[43] D. Shetty, J.M. Jeong, C.H. Ju, Y.J. Kim, J.Y. Lee, Y.S. Lee, D.S. Lee, J.K. Chung, M. C. Lee, Synthesis and evaluation of macrocyclic amino acid derivatives for tumor imaging by gallium-68 positron emission tomography, Bioorg. Med. Chem. 18 (2010) 7338–7347.
[44] Y. Gao, S. Guo, Z. Zhang, S. Mao, Y. Zhang, Y. Wang, Concise synthesis of (+)-serinolamide A, Tetrahedron Lett. 54 (2013) 6511–6513.
[45] J.H. Jorgensen, Methods for dilution antimicrobial sucseptibility tests for bacteria that grow aerobically: approved standard. NCCLS document M7–A3, Nccls (1993).