Various Novel Erythromycin Derivatives Obtained by Different Modifications: Recent Advance in Macrolide Antibiotics

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Abstract: The rapid emergence of drug resistance intensified the search for new antimicrobial agents, leading to lots of novel derivatives obtained from 14- and 15-membered macrolides by chemical modifications. Many of them exhibited enhanced antibacterial activity and expanded antibacterial spectrum. Especially some of them were found to be potent for the treatment of multi-drug-resistant bacterial infections. Besides, the other biological effects of macrolide derivatives were also found. In this article, we reviewed the recent advance in the novel macrolide derivatives designed by different structural modifications on erythronolide skeleton, cladinose and desosamine in the structures.

Keywords: Macrolides, structural modification, antibacterial activity, erythromycin-susceptible strains, erythromycin-resistanct strains, erythronolide skeleton, cladinose sugar, desosamine sugar.

INTRODUCTION

Macrolide antibiotics have been used for the treatment of infections of the respiratory tract, skin and soft tissue for more than 50 years. First-generation macrolides (e.g., erythromycin A) readily lose their antibacterial activity under acidic conditions due to degradation. And these degradation products are known to be responsible for undesirable gastrointestinal side effects. Second-generation macrolide antibiotics such as azithromycin (AZM) and clarithromycin (CAM) have been widely prescribed for infections of the upper and lower respiratory tract because of their superior antibacterial activity and pharmacokinetic properties compared with first-generation macrolides. The therapeutic utility of these macrolides has led to rapid increases in the resistance rates of bacteria isolated clinically. The molecular mechanisms of bacterial resistance are diverse, but the commonest mechanism of resistance is mediated by *erm*-encoded methylation of 23S rRNA or *mef*-encoded efflux. Expression of an *erm*-resistant determinant in bacteria leads to production of a methyltransferase which modifies the key nucleotide, A2058, in the macrolide–lincosamide–*streptogramin* B (MLS_B) binding site, thereby conferring resistance to macrolides.

Emergence of bacterial resistance has prompted further research directed towards the discovery of third-generation macrolides (e.g., ketolides) that can effectively address the resistance and other issues associated with current macrolide regimens. Their mechanism of action has been elucidated: the C-11, 12 carbamate side chain or the C-6 side chain in the ketolides interacts with nucleotide A752 directly in domain II of the 23S rRNA in addition to the main interaction of the drugs in domain V. This results in tighter binding to ribosomes, and imparts some activity against methylated ribosomes in some species.

During the continuous investigation on the modification of macrolides, many derivatives were found to possess enhanced antibacterial activity, improved pharmacokinetic properties, expanded spectrum of activity and attenuated gastrointestinal side effects. Especially, some of them even showed good activity against macrolide-resistant bacteria and were regarded as leading compounds for new drugs. In this article, the research advance in the modification of macrolide antibiotics in recent years were reviewed.

THE MODIFICATION OF 14- AND 15-MEMBERED MACROLIDE ANTIBIOTICS

1 The Modification of Erythronolide Skeleton

Recent discoveries concerning the structure-activity relationships (SARs) of erythromycin A derivatives arouse people to design many series of novel macrolide analogs that mainly derived from modification of macrolactone skeleton, giving us a fresh sight to find more optimal compounds with better activity.

1.1. 3-O-Descladinosyl Derivatives

The discovery that the cladinose moiety of erythromycin A is not absolutely necessary for good antibacterial activity has opened up new areas for exploring the SARs of the macrolactone ring. Richard L. Elliott and his colleagues [1] firstly reported that 3-deoxy-6-*O*-methylerythromycin A analogs (**1a**) had moderate antibacterial activity against Gram-positive organisms, demonstrating that other functionalities besides a ketone can substitute for the 3-cladinosyl residue as well. The lower *in vitro* activity of the 3-deoxy series compared with that of the ketolides inspired them to focus on the analogs containing a planar (non-keto) sp^2-carbon at the C-3 position of the macrolactone ring. Consequently, a series of 3-*O*-descladinosyl-2,3-anhydro-6-*O*-

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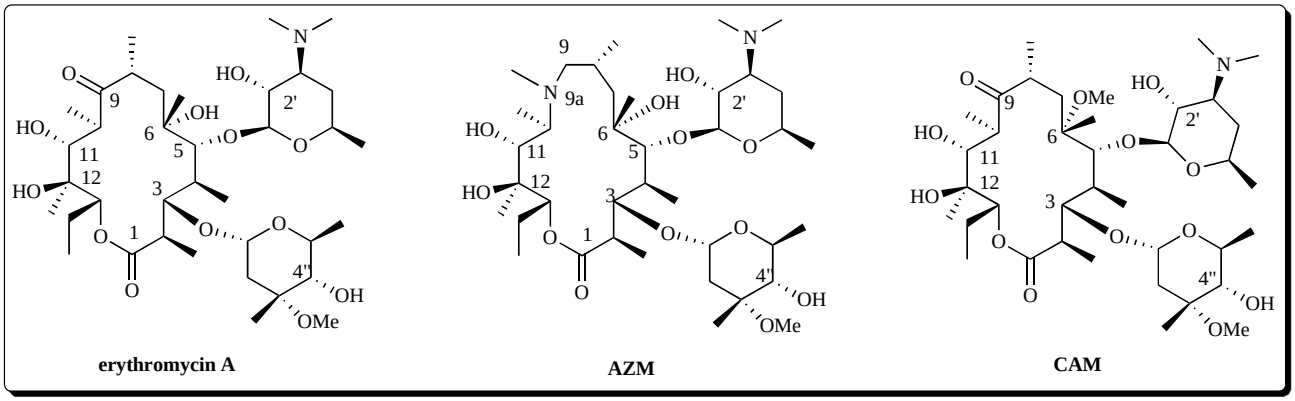
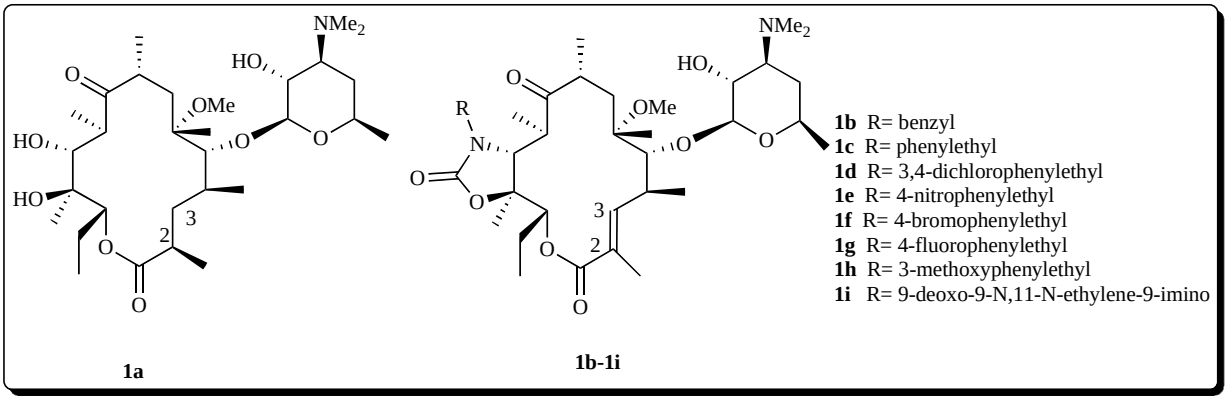
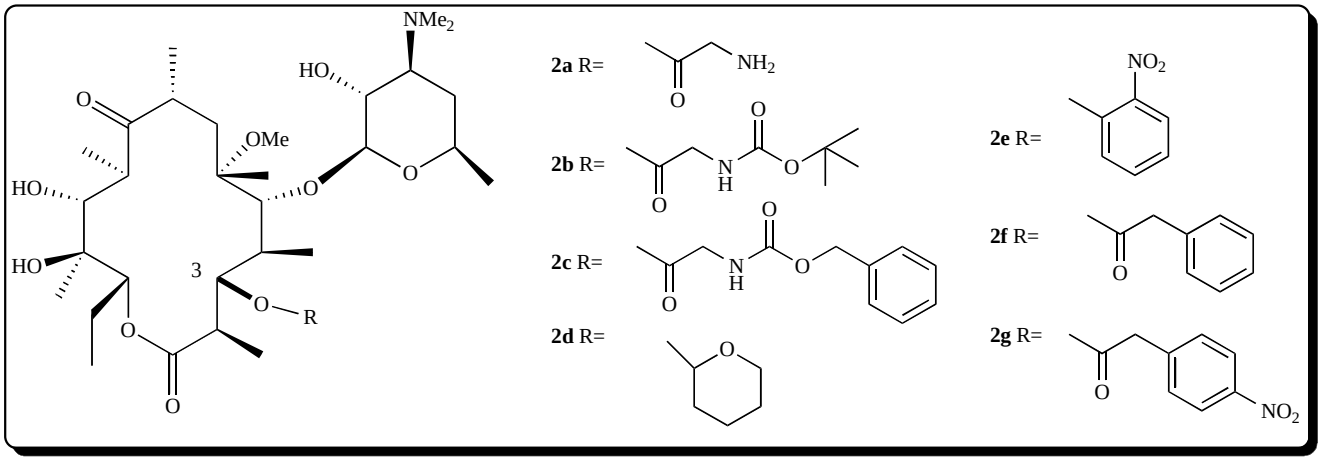
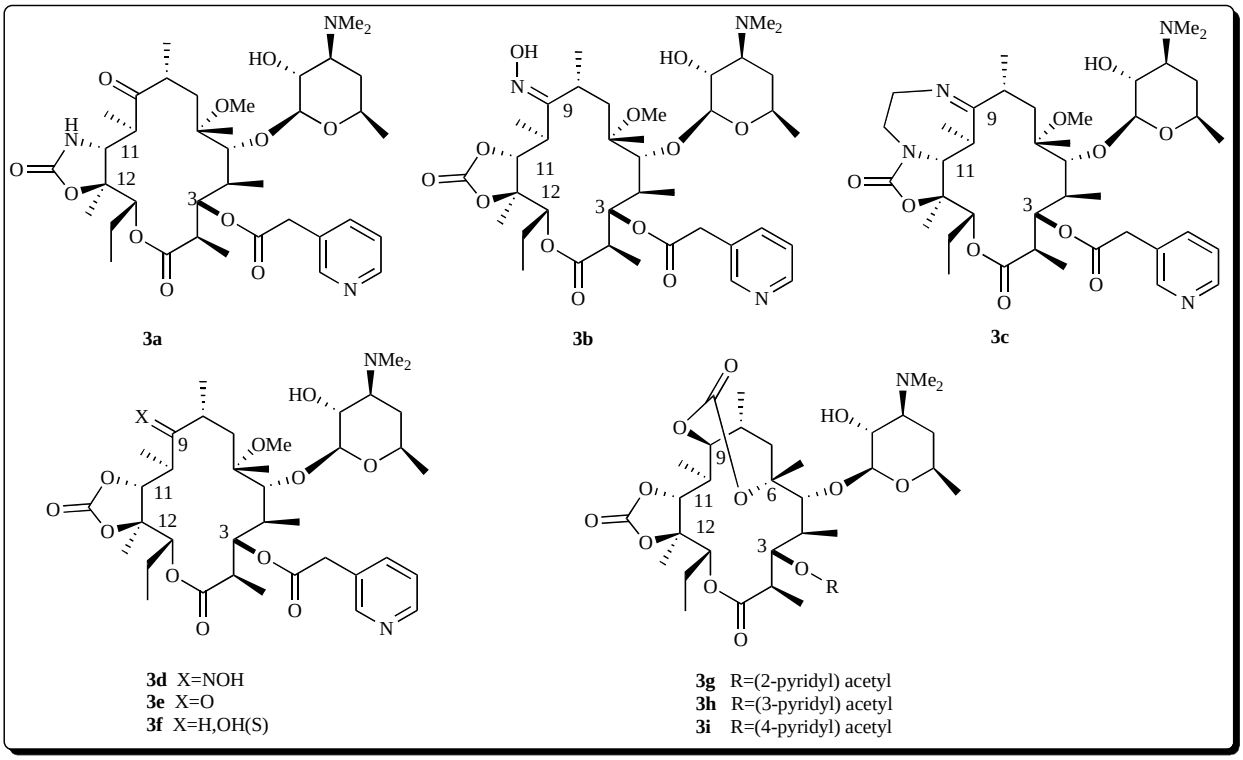




methylerythromycin A 11,12-carbamates (**1b–1i**) were synthesized and evaluated as minimum inhibitory concentration (MIC). Nearly all of them were found to be potent antibacterial agents against Gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus pneumonia* (MIC < 1 μg/mL), and some of them (**1c–1h**) showed improved activity compared with erythromycin A against the inducibly MLS_B-resistant organisms. What's more, some compounds (**1d–1h**) which demonstrated moderate antibacterial activity against the constitutively resistant *S. aureus* A-5278, *S. pneumoniae* 5979 and *S. pyogenes* 930 displayed moderate *in vivo* activity in mouse protection studies as well. Their SARs revealed that the arylalkyl side chains with two or four carbon atoms between the aromatic moiety and carbamate nitrogen possess the best *in vitro* activity.

Subsequently, introduction of an acyl group into the C-3 position of 3-*O*-decladinose-6-*O*-methylerythromycin A brought in a novel class of erythromycin derivatives named as "acylides" (**2**) [2]. The acylides proved good activities against Gram-positive pathogens, especially MLS_B-resistant strains and efflux-resistant strains. Among them, compound **2g** (TEA0777) exhibited significantly potent activity against not only erythromycin-susceptible *S. aureus* 209P-JC (MIC = 0.2 μg/mL, 250-fold greater activity than its parent acetate), but also inducibly MLS_B-resistant *S. aureus* (MIC = 0.39 μg/mL) and efflux-resistant *S. pneumoniae* 210 (MIC = 0.2 μg/mL). It has been demonstrated that the phenylacetyl





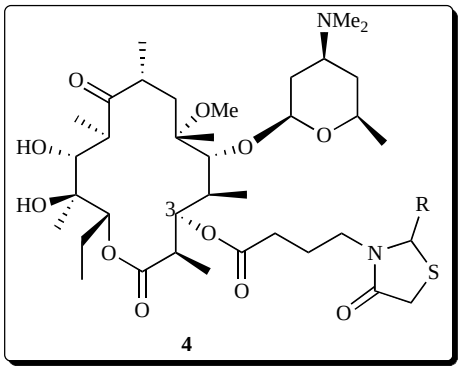
group is a promising mimic for L-cladinose at the C-3 position. Therefore, acylides are innovative semisynthetic macrolides that are potential as next-generation macrolide antibiotics.

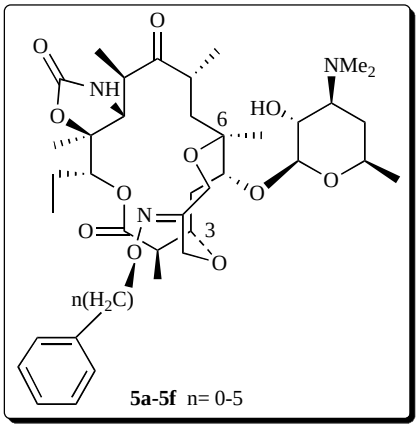
Based on the previous work, Tetsuya Tanikawa [3] proceeded with the research of the "acylides" and designed another novel series of 3-*O*-(3-pyridyl)acetylerythromycin A derivatives (**3**) that had fairly improved activity against *H. influenzae*. In particular, 6,9; 11,12-dicarbonate acylide **3h** (FMA0122, MIC = 0.78 μg/mL) was 2-fold more active than AZM, whereas its *in vivo* efficacy was moderate in the mouse protection tests. It's worth noting that 11,12-carbamate acylide **3a** (TEA0929) displayed potent activity against the main causative pathogens of community-acquired pneumonia (CAP) including the inducibly MLS_B-resistant *S. aureus* B1 (MIC = 0.39 μg/mL) and efflux-resistant *S. pneumoniae* 210 (MIC = 0.10 μg/mL). It also had an excellent mouse protection effect comparable to second-generation macrolides. The encouraging *in vivo* results for these acylides warrant further investigation to overcome MLS_B-resistant pathogens and to develop potential next-generation macrolides.

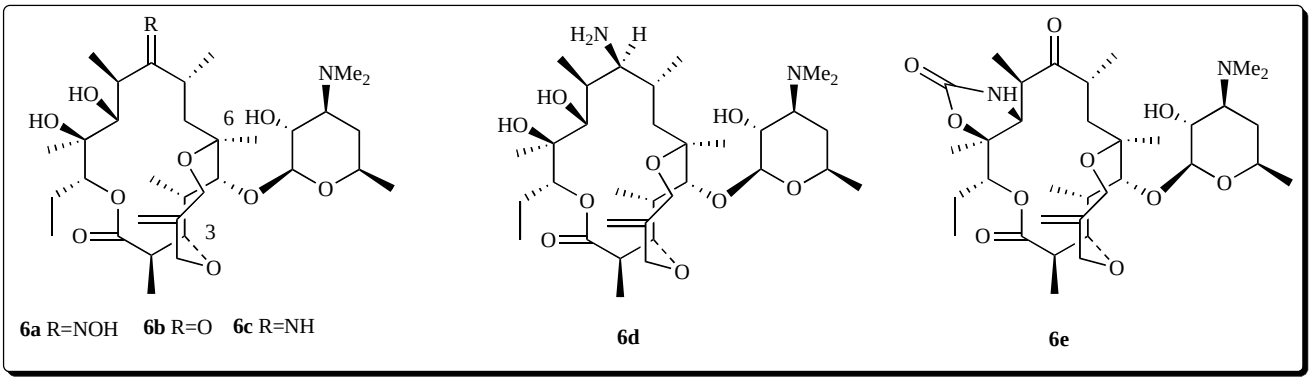
After acylides were identified as a promising class of macrolide antibiotics, new acylides 3-*O*-[γ-(4-oxo-2-aryl-thiazolidin-3-yl)butyryl]erythromycin A derivatives (**4**) were obtained by Deepa Pandey [4]. As a result, they were very active against erythromycin-resistant strains comparable to telithromycin.

1.2. 3,6-Bicyclolides

Ground on the 6,11-bicyclolide, an unprecedente series of 3,6-bicyclolide oximes (**5**) were designed and prepared by Tang [5]. These compounds with linkers of varying lengths to the secondary binding site were tested against a panel of representative respiratory pathogens, including various macrolide-resistant and multidrug-resistant strains. Compared





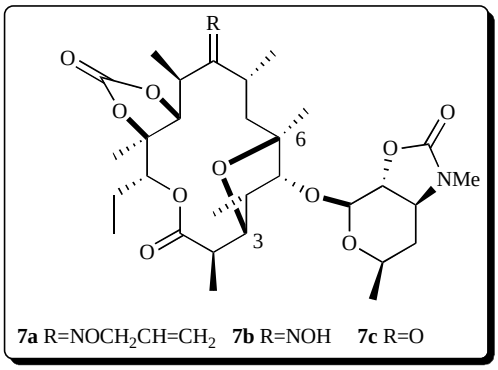


6a R=NOH **6b** R=O **6c** R=NH **6d** **6e**

with erythromycin A, all of 3, 6-bicyclolide oximes (**5a–5f**) displayded good activities against the susceptible strains (MIC ≤ 0.25 μg/mL), the *mef*-resistant strains (MIC ≤ 0.125 μg/mL), and *H. influenzae*. These results strongly suggested that each of the 3, 6-bicyclolide oximes was a good template for further modifications.

Tang′s group [6] went on researching the modification of the 3,6-bicyclolide oximes and got other five new compounds (**6**). Compared with erythromycin A, all of the novel 3,6-bicyclolides demonstrated significant improvement in activity against erythromycin-resistant *S. pneumoniae* (MIC ≤ 0.25 μg/mL), *S. pyogenes* (MIC ≤ 0.5 μg/mL) and MLS_B-resistant *S. aureus* (MIC ≤4 μg/mL). Moreover, compound **6e** retained activity against *H. influenzae*. In acute systematic infection model in mice, the compound **6e** demonstrated 2- to 3-fold improvement in efficacy compared with telithromycin against macrolide-susceptible *S. aureus Smith*, and *mef*-encoded *S. pneumoniae* (ED_{50} = 10mg/kg and 7mg/kg, respectively). In general, the newly developed 3,6-bicyclolides (especially **6e**) displayed excellent *in vitro* and *in vivo* activities against a broad spectrum of bacteria including resistant respiratory tract pathogens.

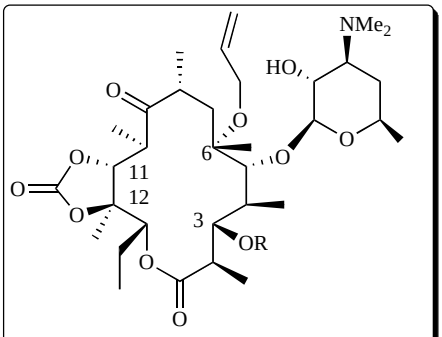
In addition, erythromycin A was converted into a 3,6-bridged ether *via* a C-3 chloroformate by nucleophilic addition of the hydroxyl group at C-6 position and then was subjected to further transformations to afford *N*-demethyl-3-*O*-descladinosylerythromycin A 2′, 3′-carbamate-11,12-carbonate-3,6-ethers (**7**). But they were inactive within the limits of the analysis, indicating that the structural unit lowered the antibacterial activity due to loss of the basic dimethylamino group [7].



7a R=$NOCH_2CH=CH_2$ **7b** R=NOH **7c** R=O

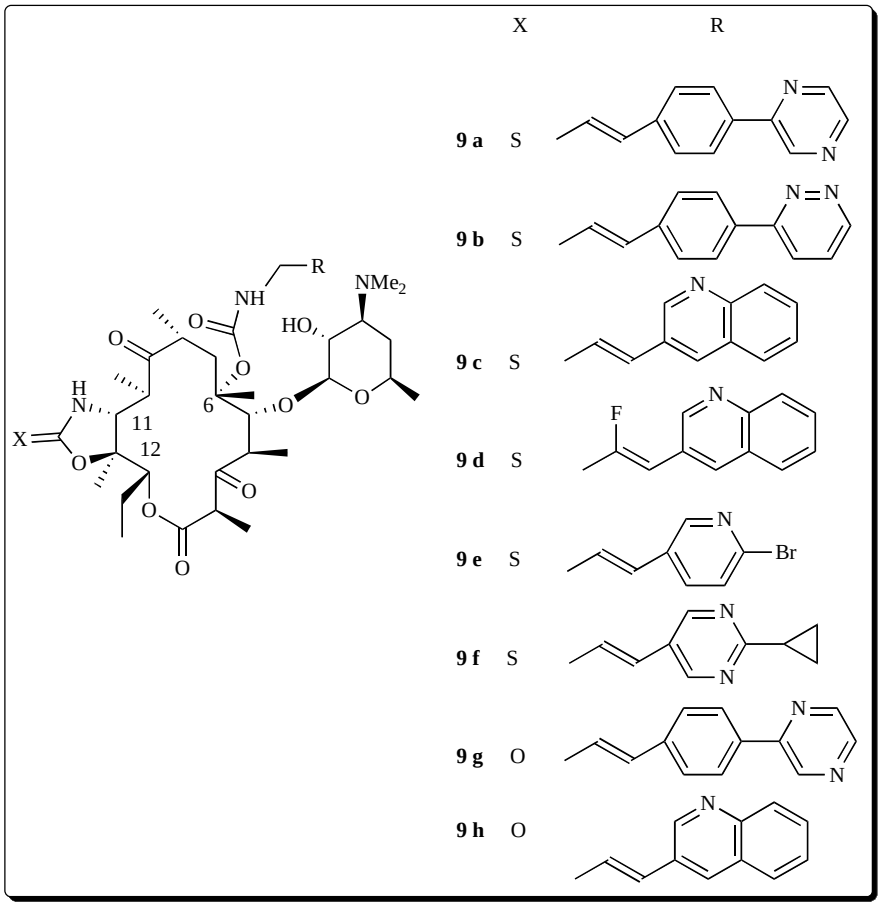
1.3. 6-O-Substituented Derivatives

The C-6 position of macrolides is another important modification site which should be emphasized. As a result, a notable series of 6-*O*-allylic acylide derivatives (**8**) were obtained from erythromycin A *via* a facile procedure such as cyclic carbonation to C-11,12 positions, acylation to C-3 hydroxyl and deprotection. These compounds showed antibacterial activity against both methicillin-susceptible or methicillin-resistant strains and erythromycin-susceptible or erythromycin-resistant strains. Among them, compounds **8a** and **8h** exhibited significantly improved activity compared with CAM. The results implied that the introduction of an arylacetyl group into C-3 position can enhance the antibacterial activity. Particularly, compound **8h** displayed more potent activity against susceptible Gram-positive pathogens than compound **8a** [8].



8a R=(3-pyridyl)acetyl
8b R=(3-indoly)acetyl
8c R=(2-chlorophenyl)acetyl
8d R=(3-fluorophenyl)acetyl
8e R=(4-chlorophenyl)acetyl
8f R=phenoxylacetyl
8g R=(3-indolyl)propionyl
8h R=(3,4-methylenedioxy)phenyl acetyl
8i R=(2-thienyl)acetyl

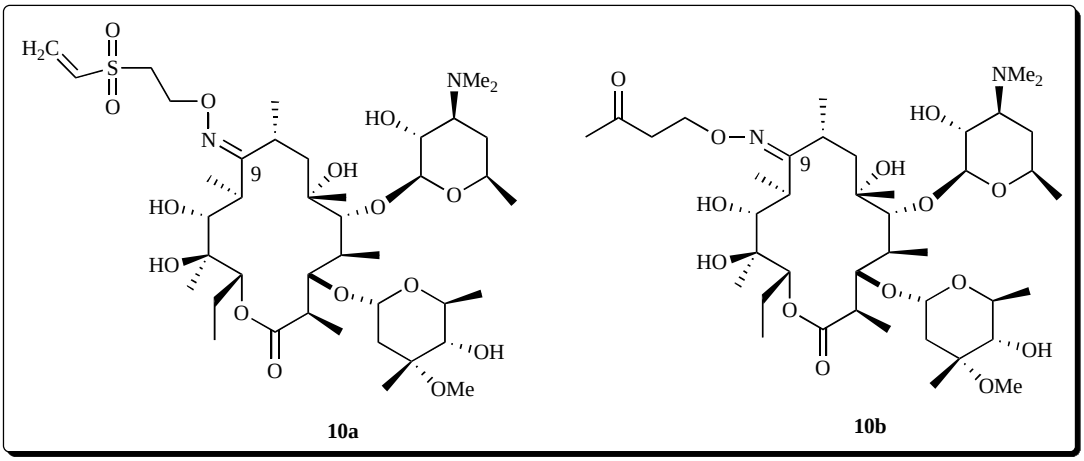
Large number of studies demonstrated that the terminal heteroaryl group of C-6-*O*-carbamoyl side chain could increase the affinity of ketolides to both macrolide-susceptible and macrolide-resistant ribosomes. On the basis of the above results, a series of 3-keto-6-*O*-carbamoyl-11,12-cyclic thiocarbamate erythromycin A derivatives (**9**) were got and evaluated for their activity against respiratory pathogens [9], and the discovery broaded our investigation of this 6-*O*-

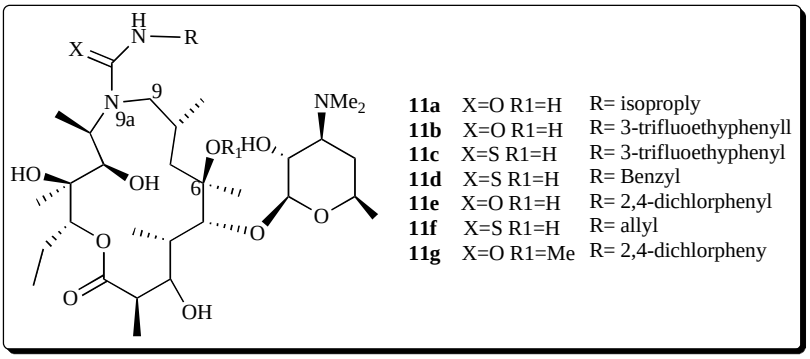


carbamoyl series. Thereamong, compounds **9c, 9g** and **9h** possessed the best *in vitro* antibacterial activity similar to telithromycin against erythromycin-susceptible *Streptococcus pneumoniae* OC9132, *Staphylococcus aureus* OC4172, *mef*-encoded *Streptococcus pneumoniae* OC4051 and efflux-resistant *Streptococcus pneumoniae* OC4438.

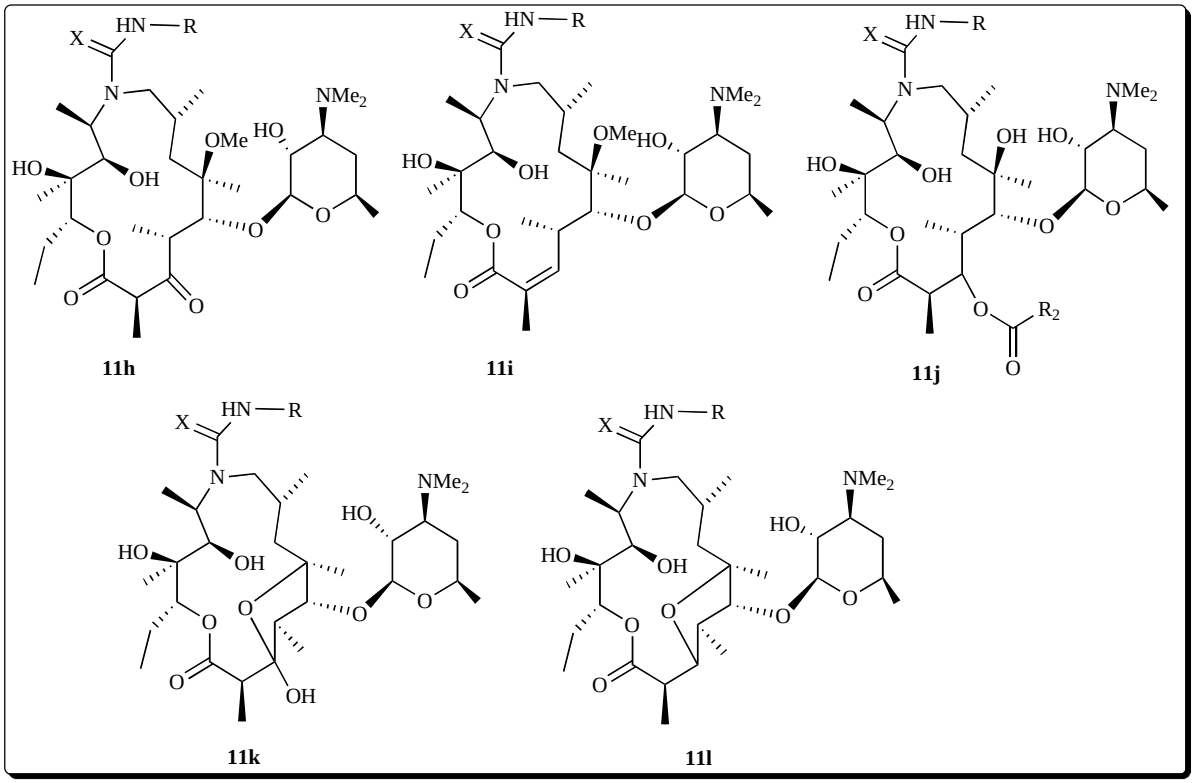
1.4 9-O-Substituented Derivatives

It is well known that erythromycin is instable and easy to lose activity in acidic condition due to the reactivity of the ketone at C-9 position and the hydroxy groups at C-6 and C-12 positions. The transformation of the ketone to an oxime is a possible way of preventing internal ketalization. Hence, Dondas H.A. [10] designed erythromycin A 9-*O*-(2-ethenesulfony-ethyl)-oxime (**10a**) and erythromycin A 9-*O*-(3-oxo-butyl)-oxime (**10b**) from erythromycin A by Michael reaction. The two compounds were found to be active in some cases against *C. diphtheriae*, manifesting that the transformation of the ketone at C-9 position of erythromycin A to an oxime resulted in a decrease of *in vitro* antibacterial activity, but the drop in activity was not so dramatic except for *S. faecalis* and *E. coli*.





11a	X=O R1=H	R= isoproply
11b	X=O R1=H	R= 3-trifluoethyphenyll
11c	X=S R1=H	R= 3-trifluoethyphenyl
11d	X=S R1=H	R= Benzyl
11e	X=O R1=H	R= 2,4-dichlorphenyl
11f	X=S R1=H	R= allyl
11g	X=O R1=Me	R= 2,4-dichlorpheny



11h **11i** **11j**

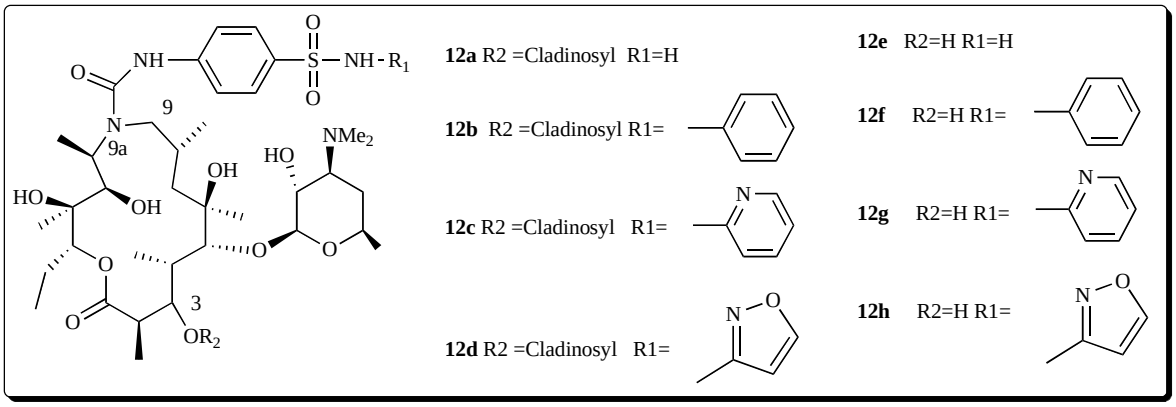
11k **11l**

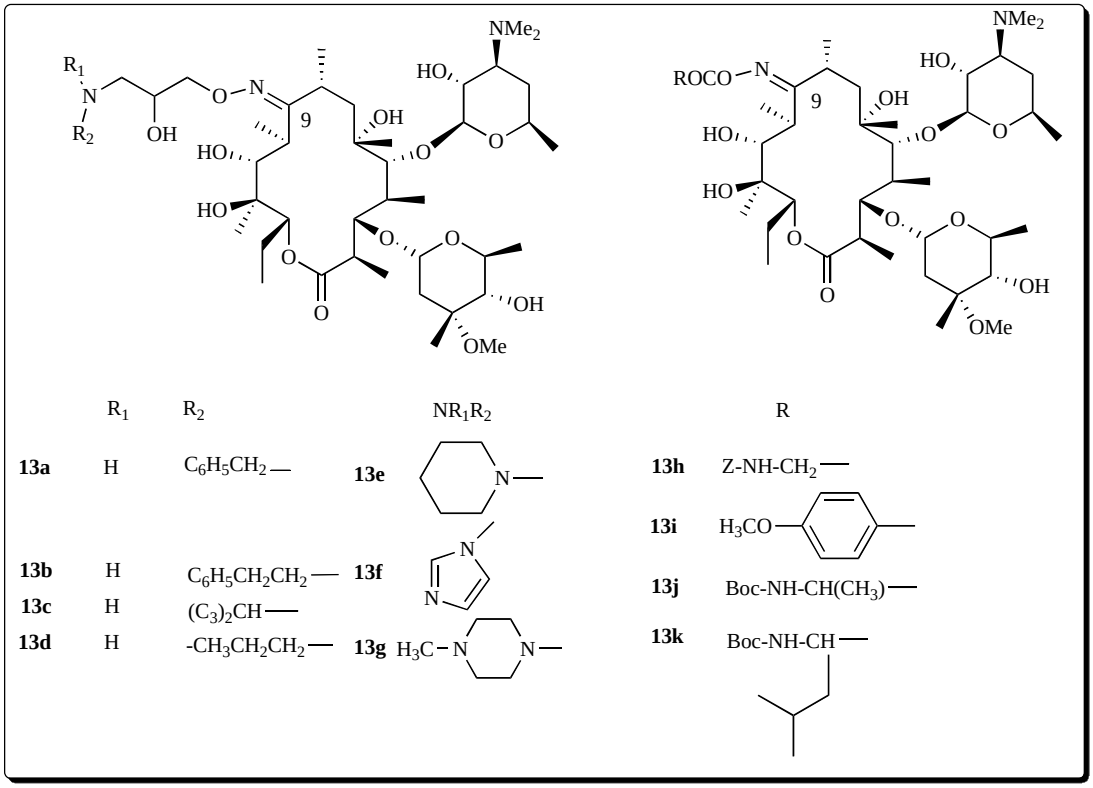
It is expected that introduction of an unsaturated unit, carbamoyl group, on nitrogen at C-9 position of azalides (e.g. AZM) may significantly change electronic properties and steric environment in the 'upper part' of the macrolide. Zorica′s group [11] developed an efficient method for the synthesis of diverse 9a-carbamoyl (or 9a-thiocarbamoyl) derivatives of azalides (**11**). The compounds (**11a–11g)** bear various alkyl and aryl groups through urea or thiourea linkage at 9a-position and their conformation in solution are C-3 to C-5 'folded out'.

Additionally, they also prepared the derivatives of ketolides (**11h**), anhydrolides (**11i**), hemiketals (**11j**), cyclic ethers (**11k**), and acylides (**11l**). However, the activity of these compounds (**11**) was undesirable, only displayed moderate activity against resistant pathogens, As the SARs of these derivatives were far less established in contrast to 14-membered analogs, the results only provided a new insight into their antibacterial activity.

Sulfonylureas of azalides with significant activity against inducibly resistant *S. pyogenes* evoked scientists to further explore modifications at 9a-position of azalides. Novel hybrid compounds (**12**) were developed by Mirjana and his colleagues [12]. Among them, the AZM-sulfonamide conjugates **12a–12d** had good activity against macrolide-susceptible *S. pyogenes* and *Streptococcus pneumoniae*, but they were found to be inactive against Gram-negative *H. influenzae*, *mef*-encoded *E. coli* and constitutively resistant *S. pyogenes.* However, the decladinosyl derivatives **12e–12h** didn′t show any antibacterial activity at all, indicating the importance of the cladinose.

In order to reveal the effect of amino alcohol ethers as well as 9-oxime esters on the antibacterial activity, Deepa Pandey [13] investigated erythromycin A oxime ethers (**13a–13g**) and esters (**13h–13k**) by opening of the epoxy linkage through various amines. These derivatives exhibited promising activity against *E. coli* (a potential hazard to human



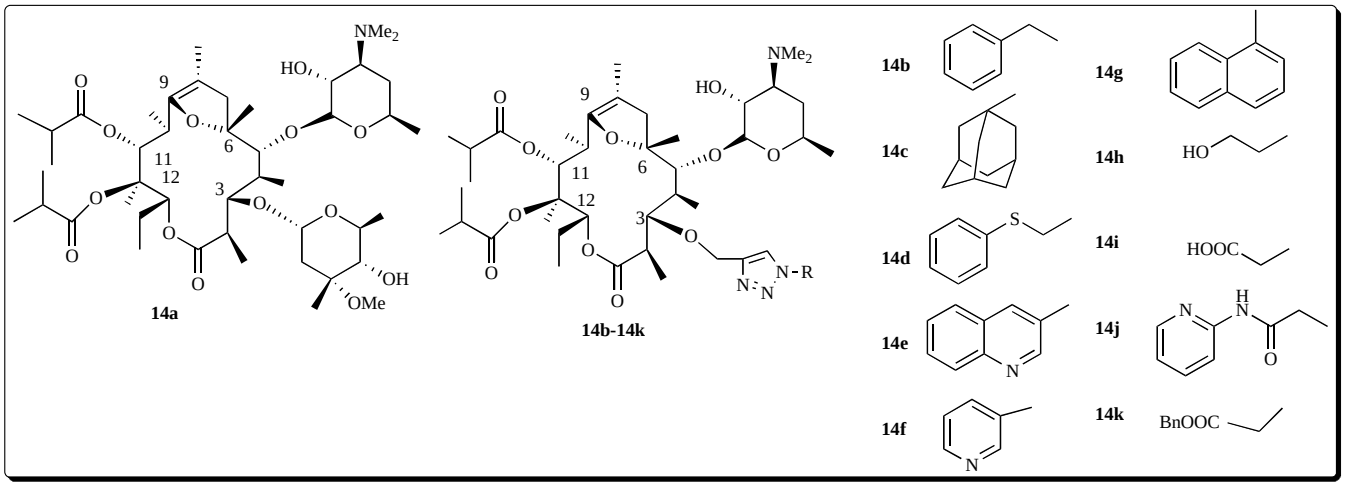


health, which is highly resistant to erythromycin A). They possessed moderate activity against *S. aureus*, *B. subtilis* and *K. pneumoniae* as well. However, the introduction of amino alcohol moiety into the macrolide skeleton did not conduce to the enhancement of antibacterial activity. Despite the activities of the compounds **13** were not as excellent as expected, the finding provided a new lead for further studies about the SARs of macrolides.

1.5. 11,12-Di-O-Substituted Derivatives

The hydroxy group C-11,12 in the vicinity of the nucleotide A752 in domain II could also be modified to strengthen the interaction with the 23S rRNA. Akihiro Sugawara and his group [14] envisioned that 11,12-di-*O*-acyl groups in macrolides were essential for anti-methicillin-resistant *Staphylococcus aureus* (MRSA) and anti-vancomycin-resistant *Enterococcus* (VRE) activity. They thus began their investigations on 11,12-di-*O*-acyl-8,9-anhydroerythromycin A 6,9-hemiketal derivatives to elucidate the SARs of anti-MRSA and anti-VRE strains. After screening various diacyl compounds, 11,12-di-*O*-isobutyryl-8,9-anhydroerythromycin A 6,9-hemiketal (**14a**) was found to be a potential agent against MRSA and VRE strains.

To obtain more potent compounds, new 8,9-anhydroerythromycin A 6,9-hemiketal derivatives (**14b-14k**) were provided by using a copper catalyzed azide–alkyne cyclization reaction, which is one of the most reliable methodologies for ideal 'click chemistry'. After the *in vitro* antibacterial test, compounds (**14b–14f** and **14i–14j**) with triazole groups instead of cladinose at C-3 position were found to exhibit anti-MRSA and anti-VRE activity. Among them, the adamantyl-triazole product **14c** was discovered as a potential lead of new antibiotic against MRSA and VRE strains (32-fold greater activity than erythromycin A).



2. The Modification of the Cladinose Sugar

There have been previous reports that introduction of some side chains at 4″-position of the cladinose sugar would bring in decreased inducing activity and had a negligible effect on antibacterial activity, and 4″-modification can alter the relative potency an antibiotic has for induction and inhibition. Consequently, many derivatives modified at 4″-position, for example, A-6056510 and CP-544372, were obtained for antibacterial activity. Especially, CP-544372 with 2-*N*-substituted aminoethyl-carbamoyl chain at 4″-position was identified effective against MLS_B-resistant strains.

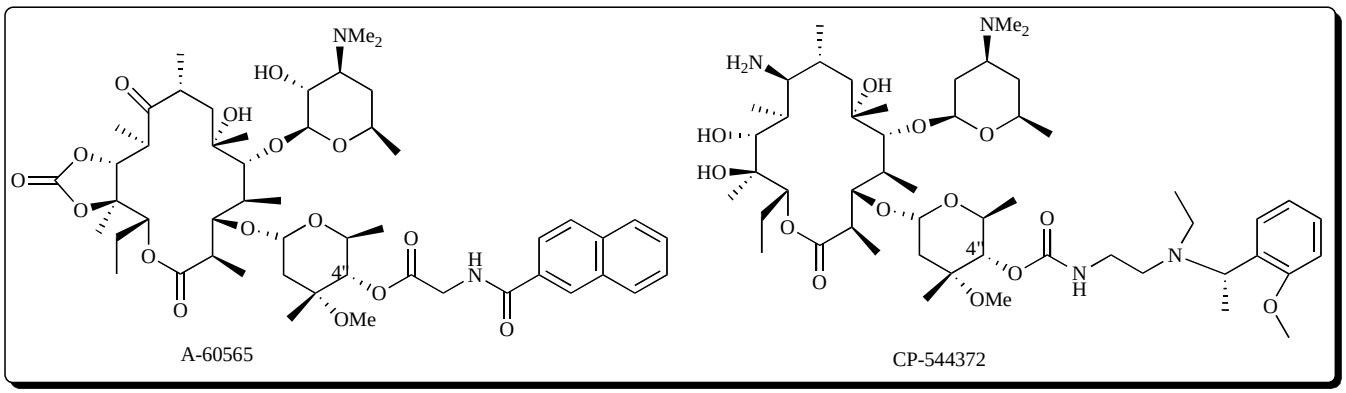
According to the result of X-ray cocrystal structure study, the prolonged 4″-arylalkyl group of CP-544372 can reach the chloramphenicol binding site (the peptidyl transferase region) and inhibit peptide formation of bacterial ribosomes, which is very informative for structure-based drug design.

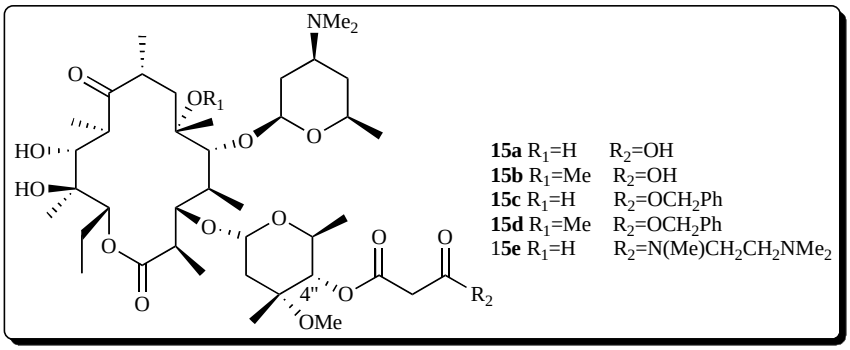
2.1. 4″-Carbonates

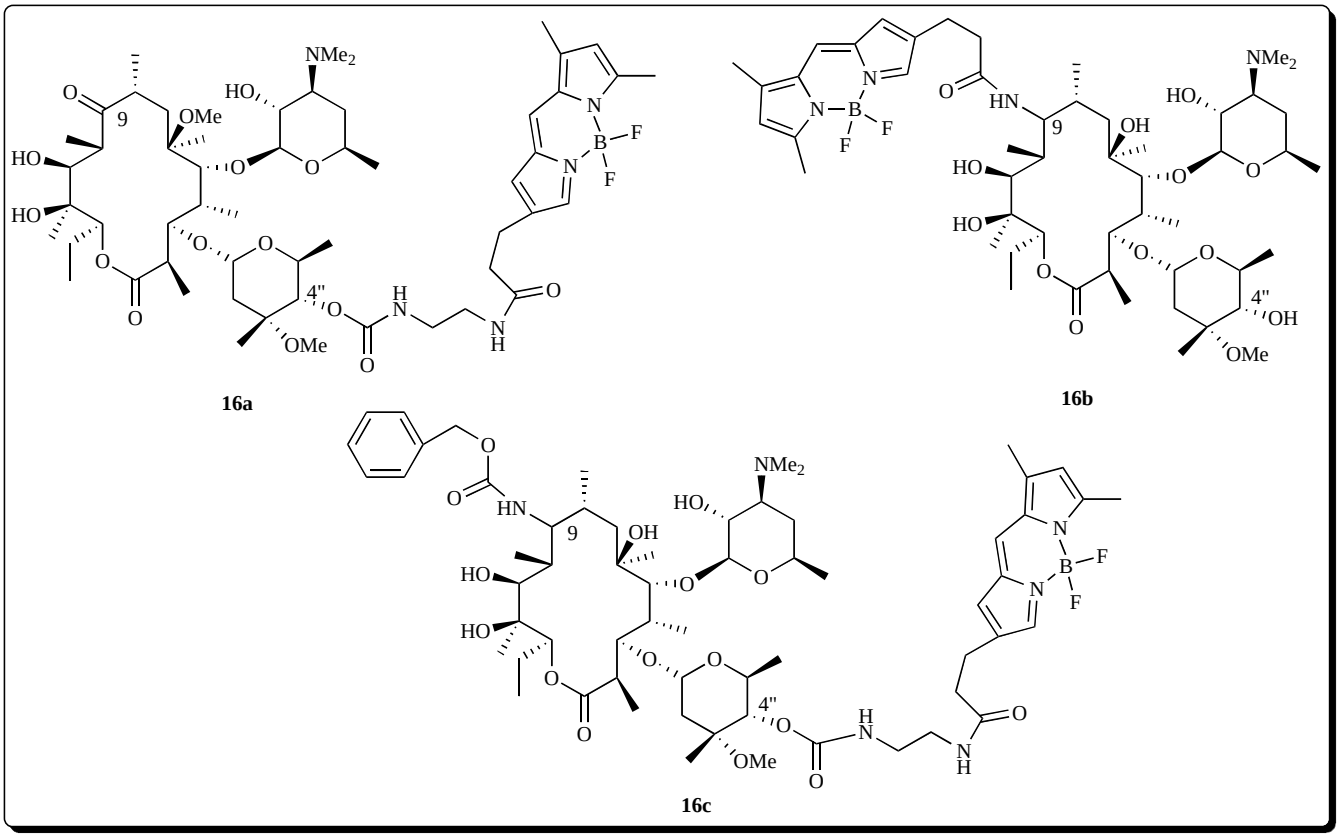
Enlightened by the crystallographic studies of ribosome-macrolide complexes, a firenew series of 4″-malonyl tethered derivatives of erythromycin (**15**) were synthesized [15]. All of them were tested for their ability to inhibit the growth of a macrolide-susceptible *E. coli* HN818 that lacks AcrAB transporter. The MIC of compounds **15c, 15d** and **15e** were somewhat higher (8 μg/mL), while MIC of compounds **15a** and **15b** were significantly higher (128 μg/mL) than the control drugs erythromycin A and CAM (2 μg/mL). Furthermore, all the compounds as protein synthesis inhibitors were tested in *E. coli* cell-free translation system. Though inhibitory activity of compounds **15a** and **15b** was reduced compared with that of erythromycin A (IC_{50} = 3.7 μM and 3.9 μM vs 0.9 μM), inhibition of translation by compounds **15c, 15d** and **15e** (1.1, 1.2 and 1.1 μM, respectively) was comparable to that of erythromycin A. Therefore, the somewhat reduced antibacterial activity of compounds **15c, 15d** and **15e** (MIC 8 μg/mL vs 2 μg/ml) should be attributed to their decreased uptake by the cell, possibly due to increased molecular weight. In contrast, compounds **15c** and **15d** with high *in vitro* activity possess bulky and relatively rigid benzyl groups that can accommodate the ribosome fairly—an observation compatible with the available crystal structures.

2.2. 4″-Carbamates

It was reported that fluorescent probes that covalently link fluorophores to ribosome inhibitors were used to probe inhibitor-ribosome interactions and to estimate the location of the inhibitor binding site. Evoked by the previous study, Li [16] introduced a fluorophore of 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diazas-indacene (BODIPY-FL) to the 4″- and 9-positions of the erythromycin A, and obtained three BODIPY–erythromycin probes of bacterial ribosomes. Among them, probe **16a** with tight binding affinity exhibited a roughly equivalent inhibition compared with erythromycin A. Similarly, probes **16b** and **16c** possessing low affinity showed reduced inhibition, accordingly. Nonetheless, probe





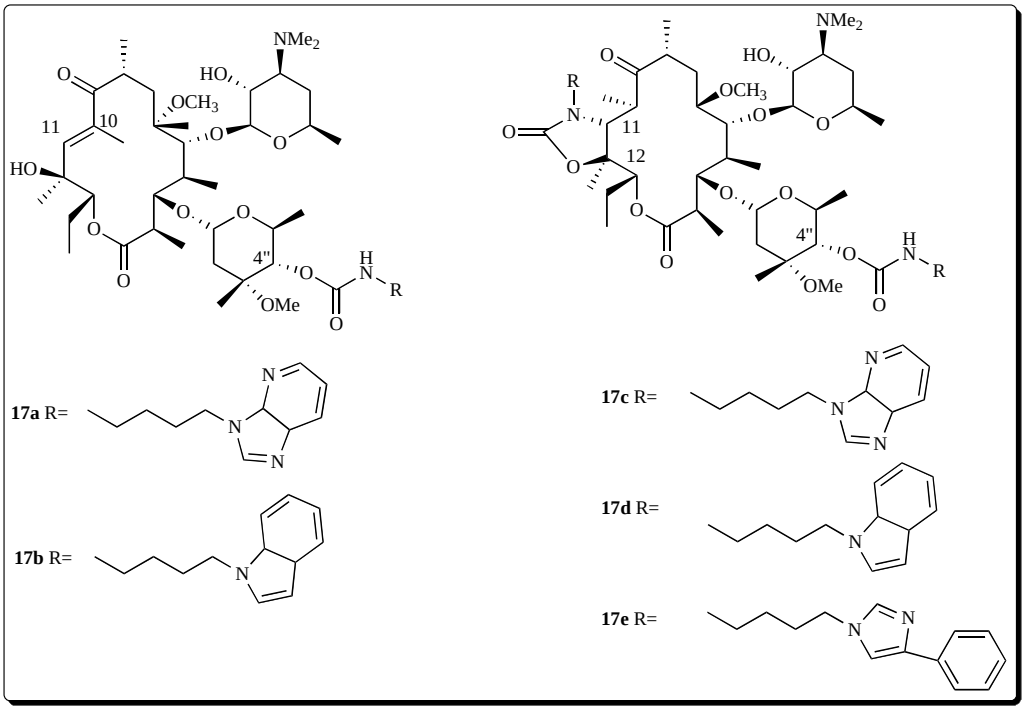


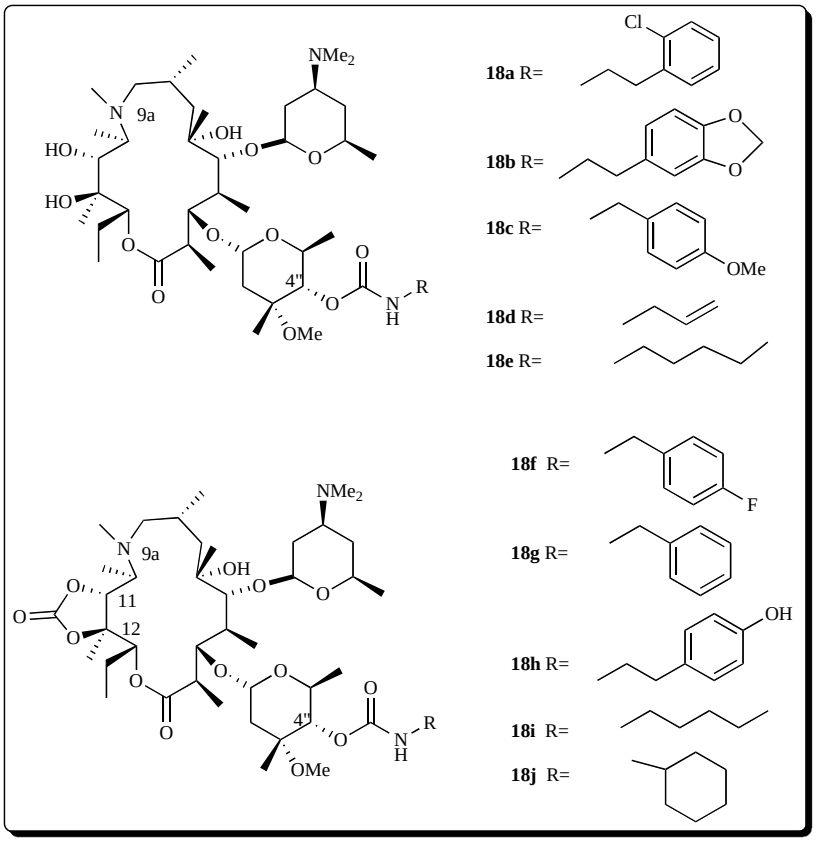
16b was successfully used to identify a series of novel ribosome ligands that competitively or allosterically displace the fluorescent probe from the bacterial ribosome. In particular, probe **16a** was found to be ideal for use in an ultra high-throughput screening to identify novel small molecules. These small molecules are being evaluated as potential start-points for chemistry optimization efforts toward the development of novel antibacterial drugs.

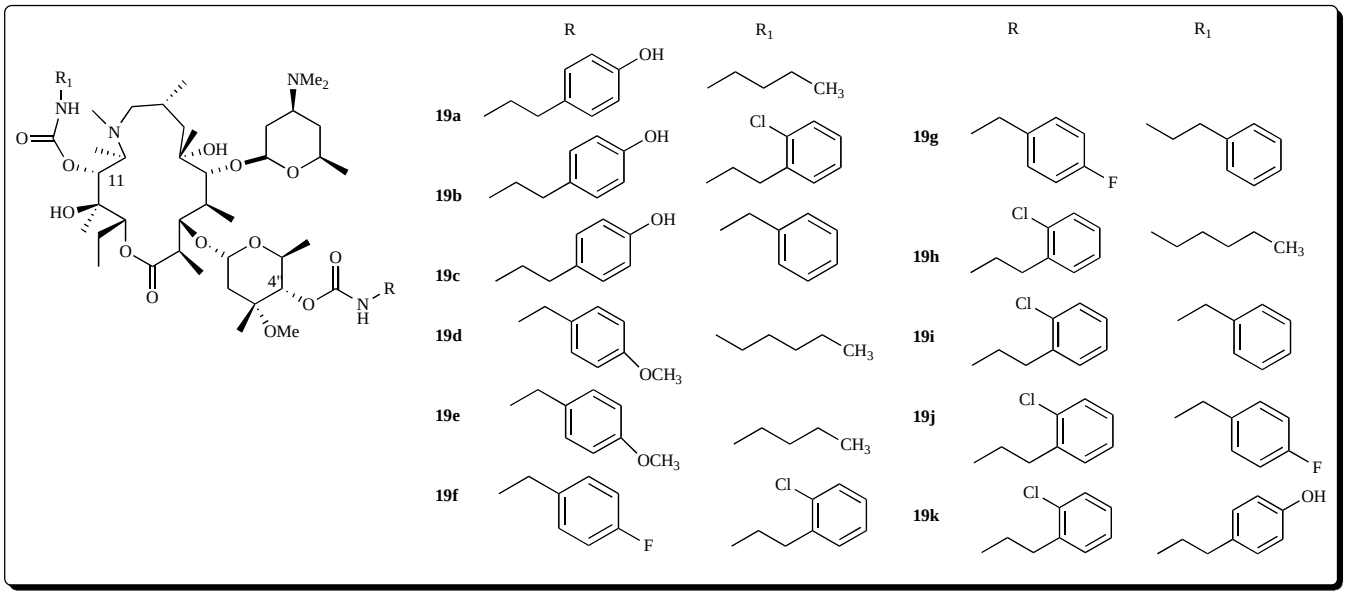
The prolonged 4″-arylalkyl side chain of CP-544372 reaches the chloramphenicol binding site and inhibits peptide formation of bacterial ribosomes, which is very informative for structure-based drug design. According to the above thought, A series of 4″-*O*-heteroarylcarbamoyl derivatives (**17**) were obtained by Xu′s group [17]. All the compounds showed improved activity against MRSA 01-433, 01-429 and 01-483, but had markedly decreased activity against methicillin-suspectible *Staphylococcus aureus* (MSSA) except for compound **17a.** It seemed that the modification on 4″-position expanded an existing antibacterial activity of the macrolides. The improved antibacterial activity against resistant bacteria possessed by these derivatives was due to the possible interaction of the arylalkyl group at 4″-position with ribosome RNA bases in the exit tunnel by aromatic stacking or van der Waals (VDW) interactions.

4″-Carbamate macrolides with an aromatic side chain attached to the 4″-position of the cladinose sugar exhibited a good activity against sensitive and resistant bacteria, which opened up a new area of modification of the macrolides. In Dr. Ma′s opinion [18], the 4″-carbamate analogs seem to have a different mechanism of action from the other macrolides and can bind to the resistant ribosome by 4″-carbamate side chains to inhibit polypeptide synthesis. In addition, it

has been reported that the C-11,12-cyclic carbamate enhanced the binding affinity of macrolides to bacterial ribosomes. As a result, a series of novel 15-membered macrolide derivatives (**18**) were designed and synthesized by the modification of hydroxyl groups at C-11, C-12 and C-4″ position of AZM. Had been evaluated, all the compounds exhibited excellent activity against susceptible *S. pneumoniae*. Among them, compounds (**18a, 18b, 18f–18h**) showed better activity against resistant *S. pneumoniae*. Consequently, auther came to the conclusion that the introduction of C-11,12 -cyclic carbonate or 4″-carbamate side chain into AZM can enhance the antibacterial activity and broaden antibacterial spectrum.





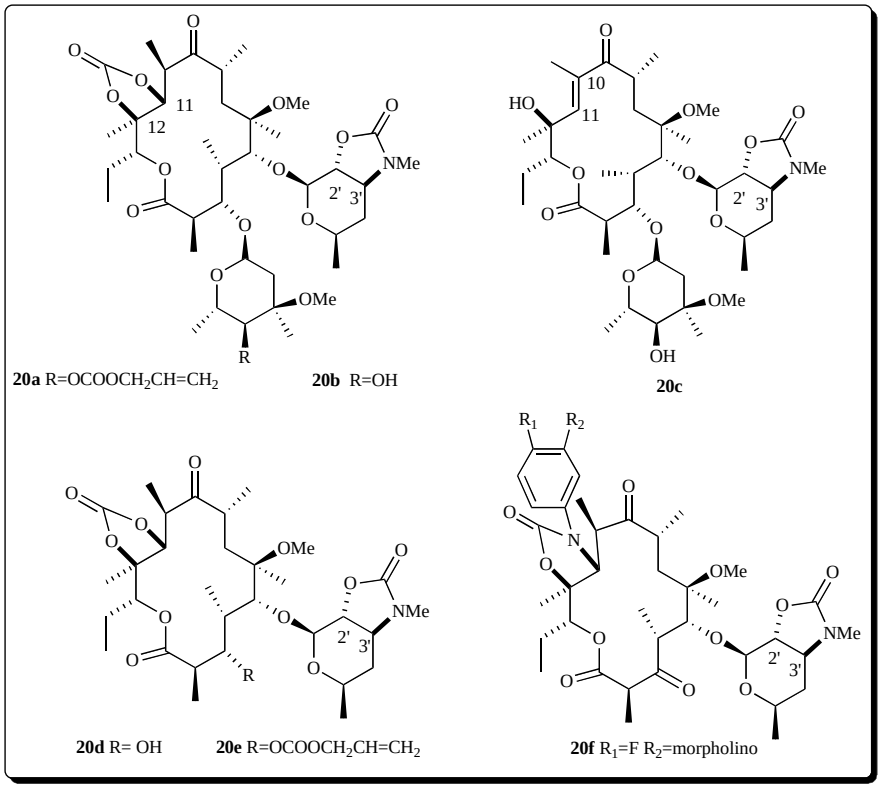


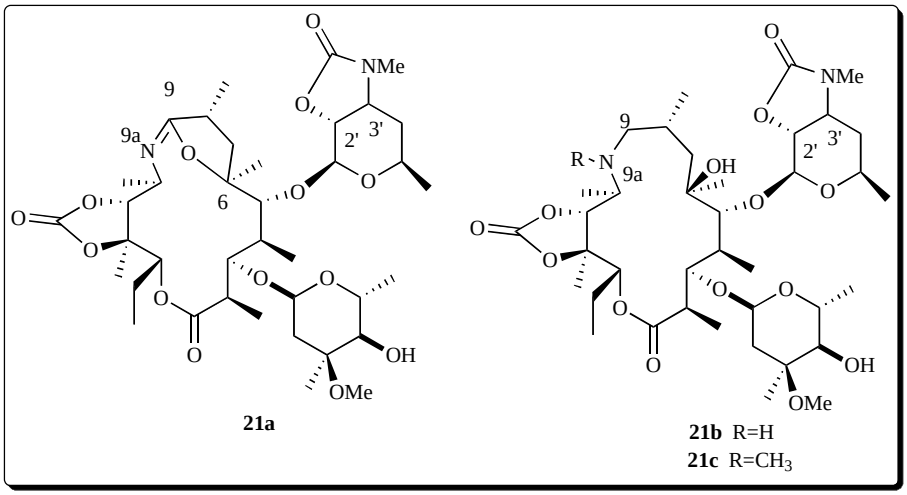
In view of the previous studies, Ma′s group [19] also developed a novel series of 4″,11-di-*O*-arylalkylcarbamoyl AZM derivatives (**19**) for *in vitro* antibacterial test. All the compounds (**19a–19k**) showed greatly improved activity (0.25–0.5 μg/mL) against *erm*-encoded erythromycin-resistant *S. pneumoniae*, exhibiting 16–32-fold greater activity, and most of the compounds still retained potent activity against *mef*-encoded erythromycin-resistant *S. pneumoniae*, compared to their precursors **18** (8 μg /mL). In contrast, the tested compounds did not show improved activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* and *mef* genes. These results indicated that introduction of 11-*O*-arylalkylcarbamoyl or 11-*O*-alkylcarbamoyl group to their precursors **18** can further enhance the activity against *erm*-encoded erythromycin-resistant *S. pneumoniae*, but do not increase the activity against *mef* or *erm* and *mef*-encoded erythromycin-resistant *S. pneumoniae*.

3. The Modification of the Desosamine Sugar

3.1. 2′,3′-Cyclic Carbamates

The cyclic 11,12-carbamate gruop is an essential part of the semisynthetic third generation macrolides and the re-





maining desosamine sugar in erythromycin seems necessary for antibacterial activity. To certify this, Audun Heggelund′s group [20] tried to substitute the C-2′ hydroxyl group in the desosamine sugar with carbonates, carbamates or ethers. They investigated the modification of the desosamine sugar and prepared a series of cyclic 2′,3′-carbamate derivatives of erythromycin (**20**). All the tested compounds were inactive within the limits of the analysis, which suggested that a basic amino group in the 3′-position of the erythromycin A is indispensable. On the other hand, a dramatic decrease in solubility in common organic solvents and water was observed for the 2′,3′-carbamate derivatives, which would expectedly be accompanied by a disturbance of the distribution and transportation of the compounds in and out of, and within bacterial cells. Hence, the lack of antibacterial activity could arise from a poor distribution in bacteria rather than from lack of ability to bind to the bacterial ribosome itself.

It seems that the macrolide antibiotics need a basic amino group for the transport within the biologic systems. Similarly, Audun Heggelund [21] also prepared cyclic 2′,3′-carbamate derivatives of AZM (**21**) to confirm the importance of a basic *N*,*N*-dimethylamino group for antibacterial activity. As supposed, the target compounds showed poor antibacterial activity against microorganisms normally sensitive to the erythromycin family, which demonstrated that introduction of a small group into the dimethylamino-alcohol moiety in the desosamine sugar would reduce interactions with the bacterial ribosome.

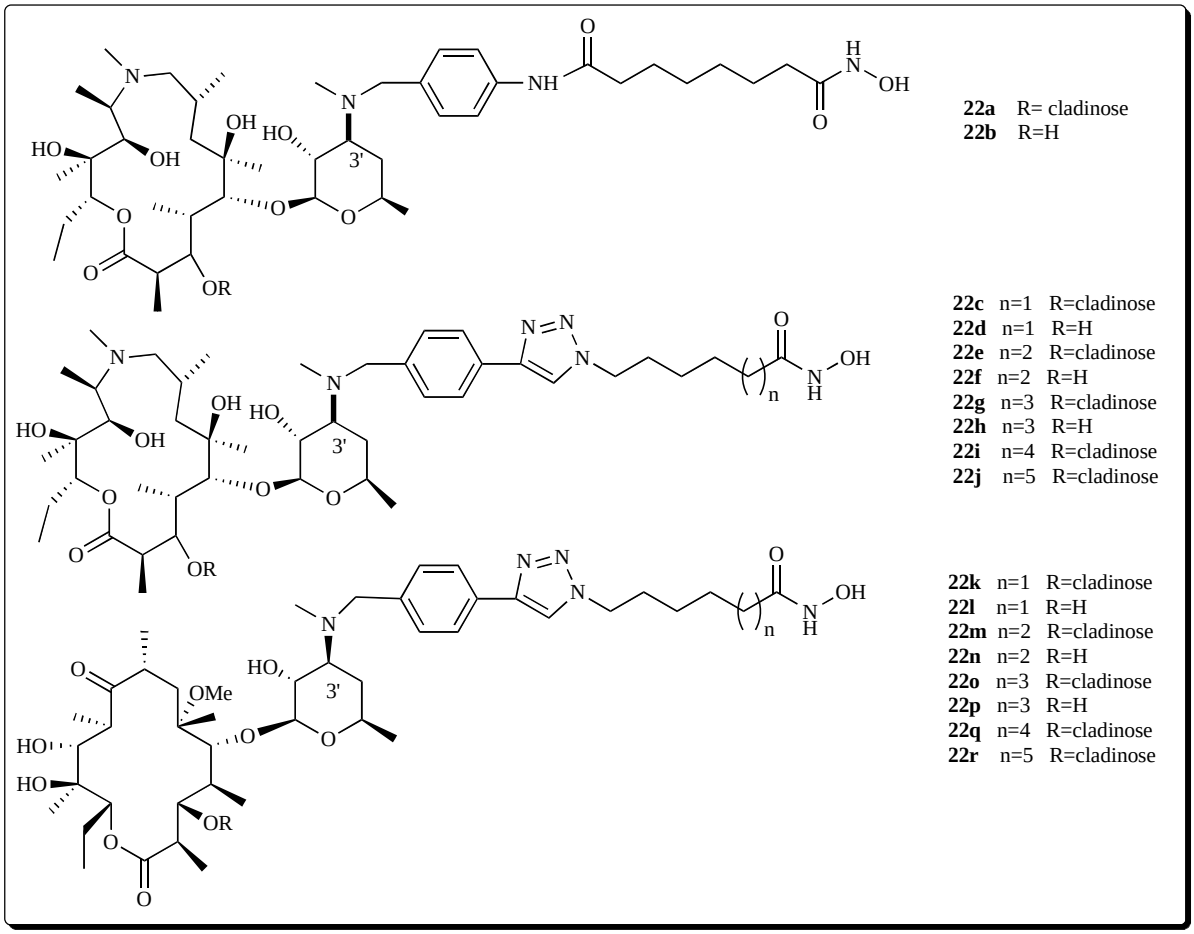
3.2. 3′-N-*Desmethyl Derivatives*

Macrocyclic depsipeptides have the most complex recognition cap-group moieties and present an excellent opportunity for the modulation of the biological activity of histone deacetylase inhibitors (HDACi). Adegboyega K. Oyelere and his colleagues [22] reported a new class of macrocyclic HDACi (**22**) based on the macrolide skeletons. The SARs studies revealed that these compounds displayed both linker-length and macrolide-type dependent HDAC inhibitory activity with IC_{50} in the low nanomolar range.

The above compounds enable a molecular description of the interaction between the HDAC enzyme′s outer rim and the inhibitors′ macrocyclic cap groups, thereby further aiding our understanding of the roles of the interaction in inhibitors′ binding affinity and possibly HDAC isoform selectivity. In addition, because the selective tissue distribution that could be conferred by the appended macrolide moiety, some of the HDACi were anticipated to have targeted anticancer activity. Specifically, the compounds incorporating AZM skeleton could be selectively accumulated in the lungs, thereby possessing lung-selective anticancer activity. The tissue-specific HDACi delivery is a particularly enticing alternative to isoform selectivity of HDACi and can lead to the identification of new chemotherapeutic agents for use in targeted cancer therapy. Efforts are underway to profile the tissue distribution of the new class of HDACi.

Meanwhile, other activities of the macrolides were also recognized at the same time. Through the changes of the substituents on nitrogen in the desoamine, nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonists (**23**) were synthesized by John T. Randolph [23]. Among them, the descladinose LHRH antagonist **23e** has 1-2nM affinity for binding to both rat and human LHRH receptors and is a potent inhibitor of LH release (pA2 = 8.76) *in vitro*. *In vivo*, **23e** was found to produce a dose-dependent suppression of LH in male castrate rats. Moreover, The oral activity of **23e** provided an advantage for this descladinose macrolide over cladinose-containing macrolide LHRH antagonists, which did not significantly effect plasma LH levels in rats when administered orally.

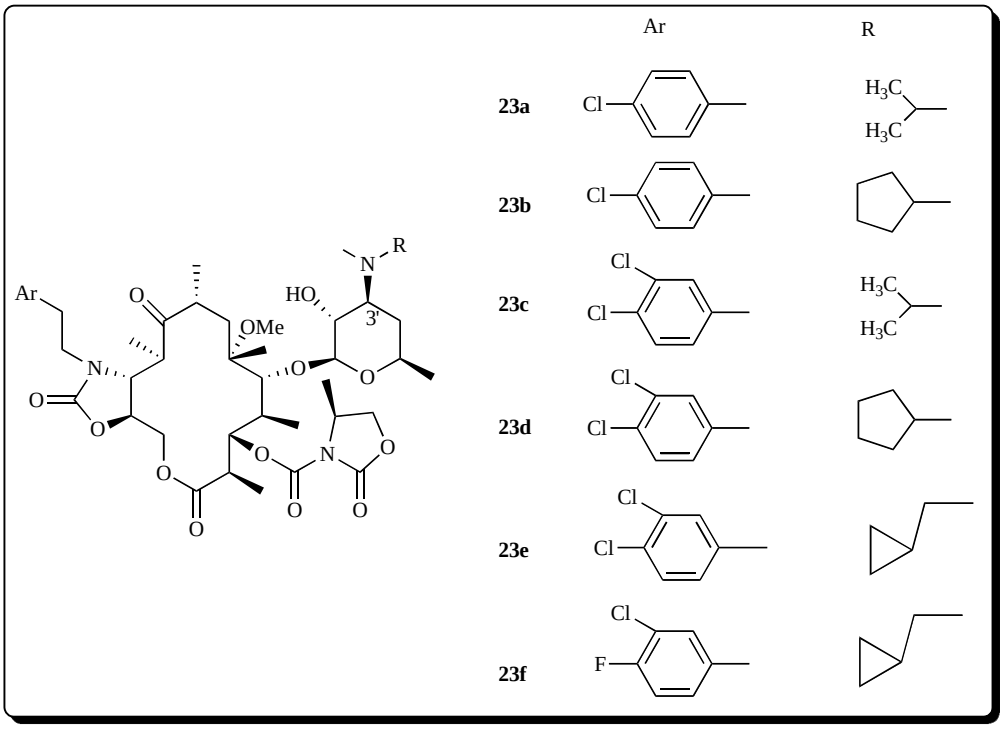
Another transformation of C-3′ amino group in desosamine sugar was took by A. Mereu′s group [24], leading to a new class of 9-(*S*)-dihydroerythromycin A derivatives (**24**). Having been tested, the antibacterial action of the macrolides (**24**) was greatly reduced or eliminated as the size of the C-3′ substituent increased. However, their anti-inflammatory properties were increased by more than 50% (e.g. compound **24g**). The best anti-inflammatory activity was obtained on amino subclass (**24d**) and amide subclass (**24f-24i**), which never showed toxicity or antimicrobial effect. These results strongly suggested the potential of macrolides as a new class of anti-inflammatory agents.

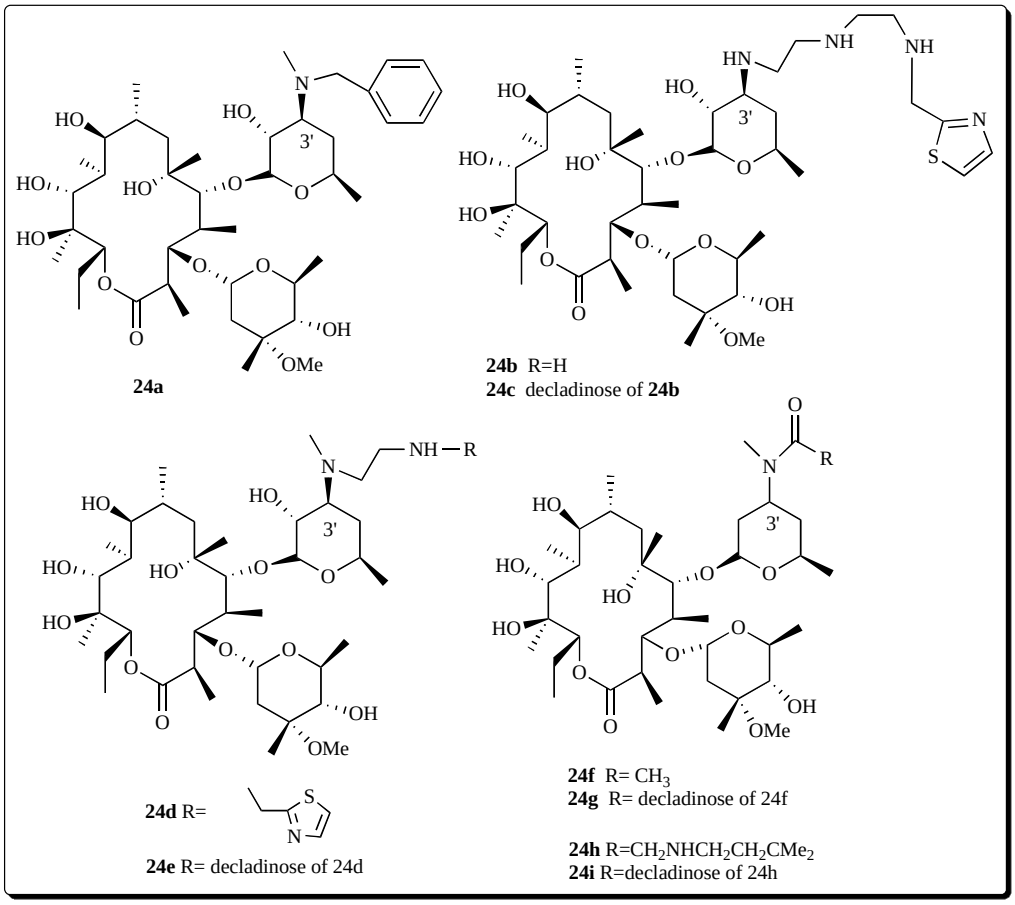


22a R= cladinose
22b R=H

22c n=1 R=cladinose
22d n=1 R=H
22e n=2 R=cladinose
22f n=2 R=H
22g n=3 R=cladinose
22h n=3 R=H
22i n=4 R=cladinose
22j n=5 R=cladinose

22k n=1 R=cladinose
22l n=1 R=H
22m n=2 R=cladinose
22n n=2 R=H
22o n=3 R=cladinose
22p n=3 R=H
22q n=4 R=cladinose
22r n=5 R=cladinose





CONCLUSION AND PERSPECTIVE

Because of increasing bacterial resistance to the existing macrolide antibiotics, the investigations in the areas of macrolides are expected to intensify. The current research efforts to overcome resistance to macrolides are focused on medicinal chemistry, and chemical modification of macrolides has been pursued by numerous investigators attempting to discover more novel erythromycin derivatives that are active against resistant strains. This approach is found to be successful and has been applied to generate novel interesting macrolide compounds which showed enhanced activities, board spectrum and other biological effects besides antibacterial activity. With further investigation on the SARs of the novel derivatives, we can anticipate the development of even more potent macrolide antibiotics for the treatment of multidrug-resistant bacterial infections in the future.

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ABBREVIATIONS

AZM	=	Azithromycin
CAM	=	Clarithromycin
MLS_B	=	Macrolide–lincosamide–*streptogramin* B
SARs	=	Structure-activity relationships
MIC	=	Minimal inhibitory concentration
CAP	=	Community-acquired pneumonia
MRSA	=	Methicillin-resistant *Staphylococcus aureus*
VRE	=	Vancomycin-resistant *Enterococcus*
BODIPY-FL	=	4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza,s-indacene
MSSA	=	Methicillin-suspectible *Staphylococcus aureus*
VDW	=	Van der Waals
HDACi	=	Histone deacetylase inhibitors
LHRH	=	Luteinizing hormone-releasing hormone

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