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Original article

Synthesis, antibacterial activity and docking of 14-membered 9-*O*-(3-arylalkyl) oxime 11,12-cyclic carbonate ketolides

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ABSTRACT

A series of 9-*O*-(3-aryl-2-propargyl)oxime ketolides **8** was synthesized and evaluated for *in vitro* antibacterial activity. Among **8**, **8b**–**8d**, and **8h**–**8l** displayed dramatically improved potency against inducibly MLS_B-resistant and efflux-resistant pathogens as compared to clarithromycin and azithromycin. Especially, **8i** (Ar=4-isoquinolyl) possessed an MIC of 0.064 μg/mL against constitutively MLS_B-resistant *Streptococcus pneumoniae*, and MICs of 0.032–0.064 μg/mL against methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus hominis*. The analog **10** with a propyl linker was less effective than both the corresponding **8** and **9** containing propynyl and propenyl linkers. A docking study was performed to gain insight into the binding mode of series **8** and **9** and to rationalize the disparity found in the SAR of **8** and **9**.

1. Introduction

The development of bacterial resistance to currently available antibiotics is a growing global health problem. Of particular concern are respiratory tract infections caused by multi-drug resistant Gram-positive pathogens. For *Streptococcus pneumoniae*, penicillin susceptibility ranged from 41.5% (Asia) to 75.3% (Europe), while susceptibility to erythromycin ranged from 23.7% (Asia) to 87.0% (Central and South America) [1]. Macrolide antibiotics have been in successful clinical use against Gram-positive pathogens for several decades. Clarithromycin, azithromycin and roxithromycin, the second-generation macrolide antibiotics, possess improved acid-stability and pharmacokinetics as compared to erythromycin (Fig. 1). However, they do not show any significant activity against bacterial isolates showing macrolide-lincosamide-streptogramin B (designated MLS_B) resistance. Recent research has revealed that the prevalence of erythromycin resistance is extremely high in Asian counties: Vietnam (92.1%), Taiwan (86%), Korea (80.6%), Hong Kong (76.8%), and China (73.9%) [2].

The resistant pathogens against MLS_B are mainly found in two genotypes: a base-specific mono- or dimethylation of 23S ribosomal RNA encoded by an *erm* gene, and acquisition of efflux pump proteins that export the macrolides outside the cells encoded by an *mef* gene [3]. In addition, MLS_B resistance can express an inducible, or a constitutive or an efflux phenotype. Ma's research clearly revealed that 3-*O*-cladinose is responsible for *erm*-mediated inducible resistance [4]

Ketolides, 6-*O*-substituted-3-keto-erythromycin derivatives, were developed to address MLS_B resistance [5–7]. Acylides [8,9], alkylides [10,11] and bicyclolides [12] are representative non-ketolides that are active against resistant bacteria. Among ketolides, telithromycin (HMR-3647) [13] has been marketed in 2001, cethromycin (ABT-773) [4] is suspended in phase-III clinical trials, solithromycin (CEM-101) [14] and modithromycin (EDP-420) [15] have entered clinical phase-II, while PF-04287881 [16] has stepped in clinical phase-I(Fig. 2). Besides a 3-keto functional group, the aforementioned compounds all possess a long chain anchored by an aryl group, which is believed to be the key factor conferring antibacterial activity by an additional secondary interaction with resistant organisms [17,18]. It is noteworthy that the sidechains of telithromycin, cethromycin, solithromycin, modithromycin and

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[2] Molecular docking.

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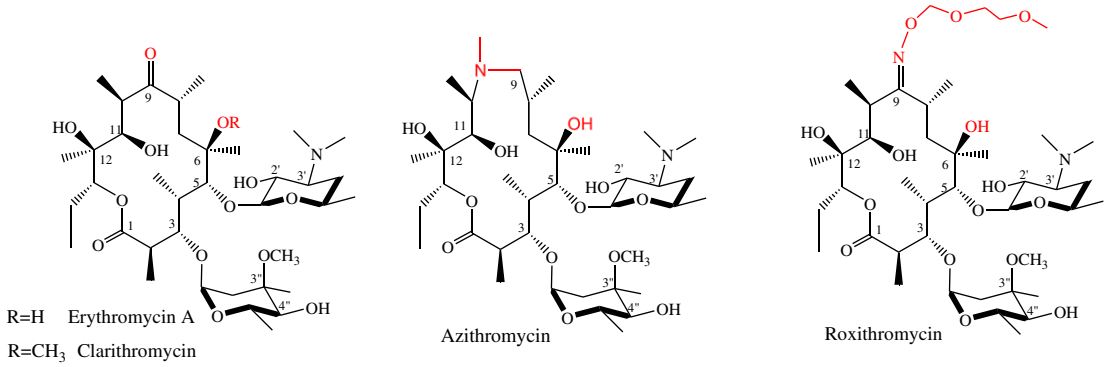


Fig. 1. Structures of erythromycin A and the second-generation erythromycin derivatives (clarithromycin, azithromycin and roxithromycin).

PF-04287881 are positioned on C-11,12, C-6, C-11,12, C-6,11 and C-11,12, respectively. Apart from these positions, 9-oxime ethers have been a point of interest, including those carrying a 3-*O*-cladinose [19–22] or carrying a 3-keto group [5,23–25]. Among them, roxithromycin [19] (Fig. 1) has been successfully marketed. Nevertheless, roxithromycin is inefficient against erythromycin-resistant pathogens. Thus, such impaired efficacy of available antibiotics requires continuous efforts to search for clinical candidates against MLS_B-resistant pathogens.

In addition to 14-membered ketolides, no promising 15-membered ketolides derived from the skeleton of azithromycin have arisen for clinical trials due to their lower activity than corresponding 14-membered analogs, although azithromycin possesses good activity against some Gram-negative pathogens [26]

As a part of our ongoing efforts to develop novel macrolides acting against erythromycin-resistant bacteria, we previously reported a series of novel ketolides bearing a 3-aryl-*E*-prop-2-enyl group attached to the 9-oxime, which resulted in a remarkable improvement against key Gram-positive resistant pathogens [27]. Further extensive study indicated the *in vitro* activity of these compounds was comparable to azithromycin against Gram-negative pathogens, such as *Haemophilus influenzae*, and *Moraxella catarrhalis* (unpublished MIC_{50} data). Triggered by this success, we herein report recent progress on the SAR of other 14-membered 9-oxime ether ketolides against a variety of clinical isolates associated with varying genotypes and phenotypes. Moreover, a molecular modeling and docking study was performed in an attempt to illustrate the potential binding site of the novel ketolides with bacterial ribosomal RNA.

2. Chemistry

The synthesis of target compounds **8** was conducted from **1** in seven steps, as shown in Scheme 1. Compound **1**, 2′, 4″-*O*-bis(-trimethylsilyl)-6-*O*-methylerythromycin A 9-*O*-(1-ethoxycyclohexyl) oxime, is the key intermediate for the scaleable synthesis of clarithromycin [28]. Treatment of **1** with dilute hydrochloric acid in ethanol yielded **2**. Next, acylation of **2** generated **3** with acetyl groups at both 2′-OH and the 9-oxime hydroxyl. As described previously [27], the acetyl group at the 9-oxime is labile and removed selectively in

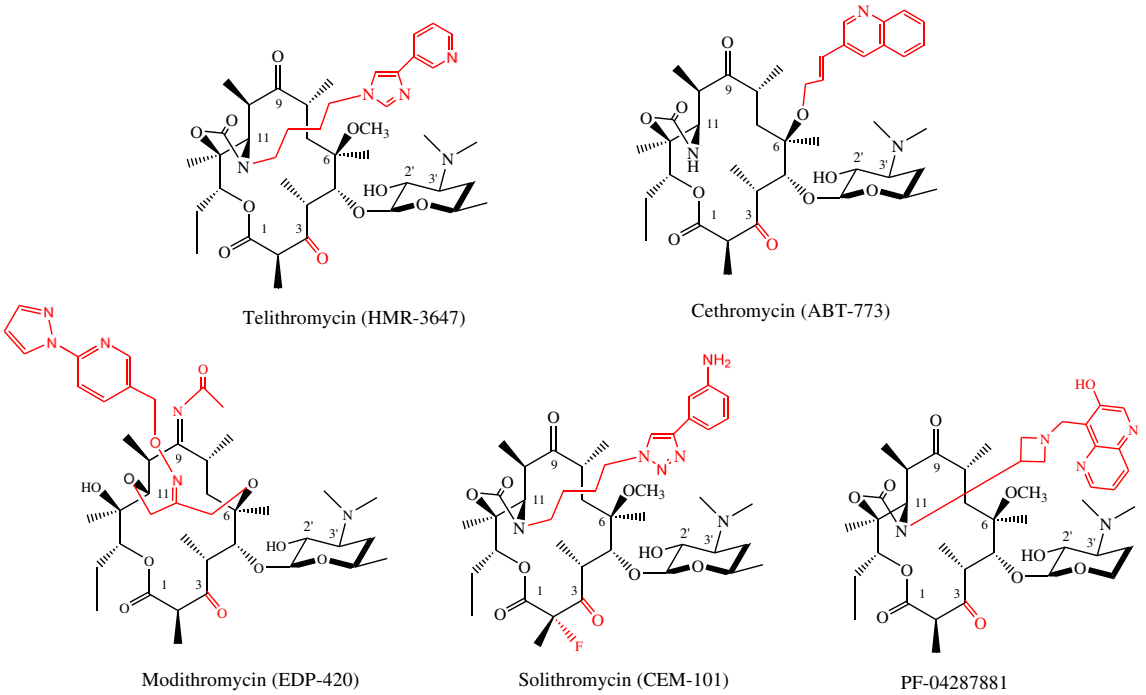
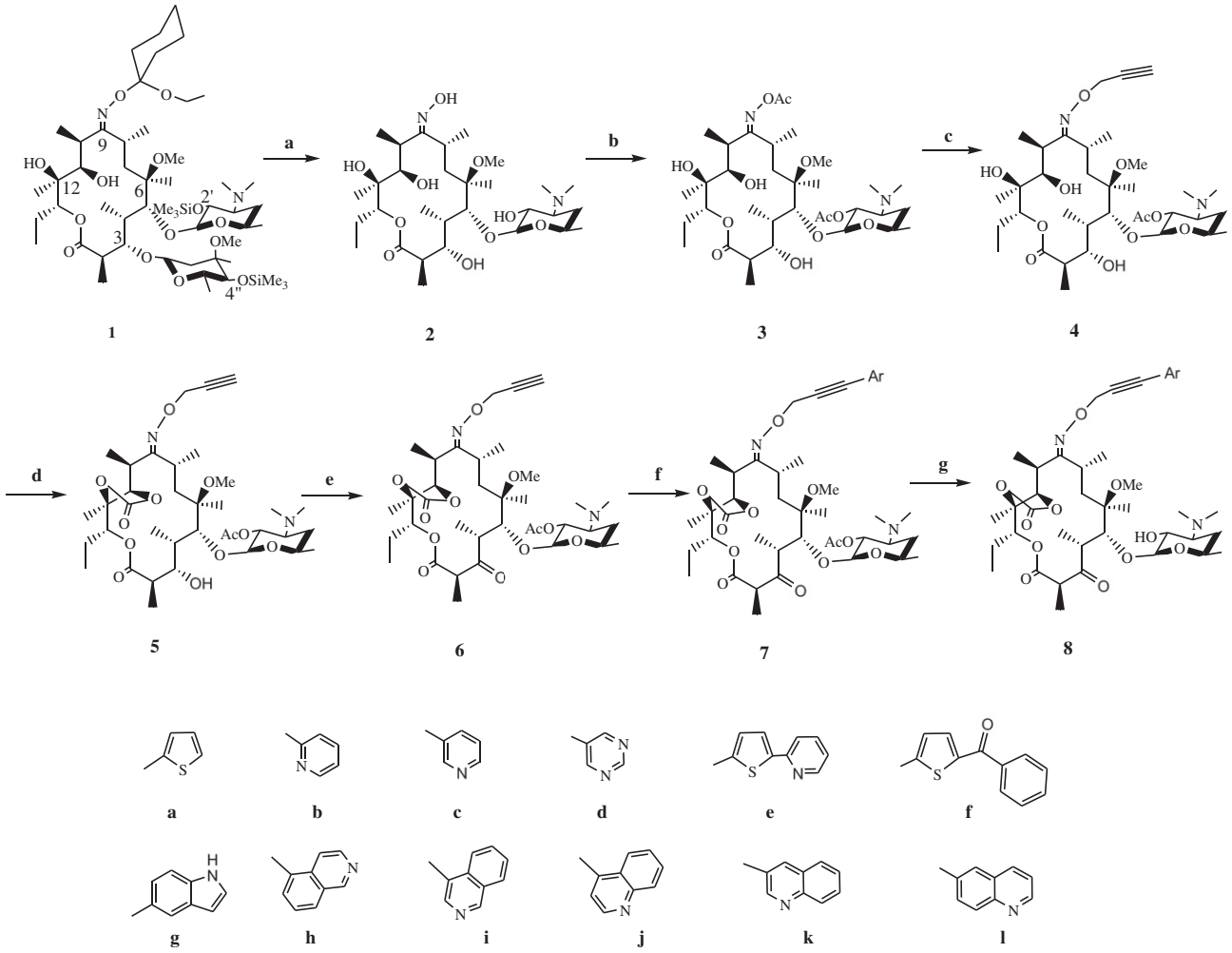


Fig. 2. Structures of the third-generation erythromycin–ketolide analogs (telithromycin, cethromycin, modithromycin, solithromycin and PF-04287881).



Scheme 1. Synthesis of the ketolides **8a**–**8l**. (a) HCl, EtOH; (b) acetic anhydride, CH_2Cl_2; (c) KOtBu, propargyl bromide, DMF; (d) pyridine, bis(trichloromethyl)carbonate, CH_2Cl_2; (e) NCS, DMS, Et_3N, CH_2Cl_2; (f) ArBr, $(PPh_3)_2PdCl_2$, CuI, Et_3N, 80 °C, 3 h, acetonitrile; (g) MeOH, 65 °C, 3 h **8a**:Ar=2-thienyl; **8b**: Ar=2-pyridyl; **8c**: Ar=3-pyridyl; **8d**: Ar=5-pyrimidyl; **8e**: Ar=2-[5-(2-pyridyl)]thienyl; **8f**: Ar=2-(5-benzoyl)thienyl; **8g**: Ar=5-indolyl; **8h**: Ar=5-isoquinolyl; **8i**: Ar=4-isoquinolyl; **8j**: Ar=4-quinolyl; **8k**: Ar=3-quinolyl; **8l**: Ar=6-quinolyl.

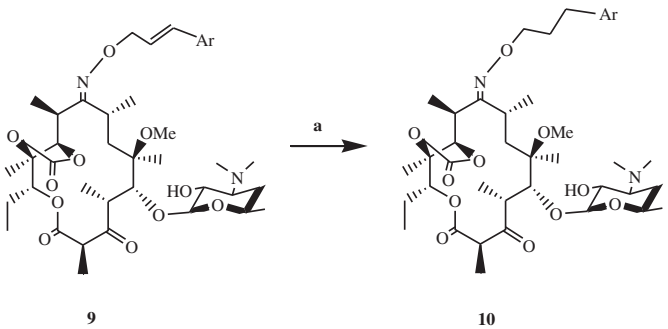
the presence of base. Thus, removal of the acetyl group at the 9-oxime and subsequent introduction of a propargyl were accomplished in a one-pot synthesis, which produced 9-*O*-propargyloxime **4**. To reach a better yield, the solvent DMF was substituted for the original THF in the synthesis of **4**.

As a 11,12-cyclic carbonate would enhance antibacterial activity [25,27], we prepared **5** by an optimized procedure for cyclic carbonylation at 11,12-OH [29]. Based on a recent investigation [30] of the stability of the Corey-Kim intermediate, we obtained 3-keto **6** in high yield and with minimal side reaction. Next, **7** was prepared by Sonogashira coupling of **6** and the appropriate aryl bromide in the presence of $Pd(PPh_3)_2Cl_2$, CuI and Et_3N in acetonitrile. Deprotection of the 2′-acetate of **7** afforded the final compounds **8**.

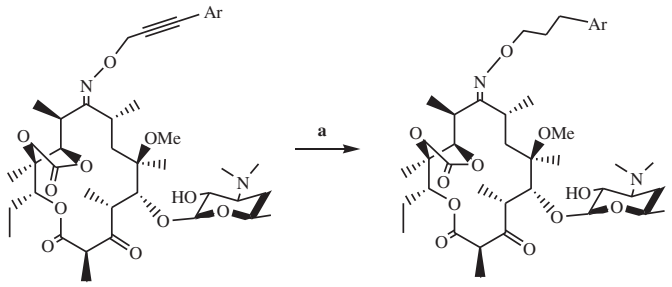
To probe the effects of side chain configuration on antibacterial activity, we prepared compounds **10k**, **10i** from **9k**, **8i**, respectively (see Schemes 2 and 3). Compound **9k** was one of the most potent ketolides bearing a 3-aryl-*E*-prop-2-enyl group at the 9-oxime against resistant bacteria [27]. Hydrogenation of *E*-olefin **9k** in the presence of 10% Pd–C and acidic medium yielded the saturated side chain **10k**. In a similar way, the hydrogenation product **10i** was obtained from **8i**, one of most effective ketolides bearing a 3-aryl-2-propargyl group discussed in this paper. Unfortunately, the desired Z-olefin **11i** was not produced at low temperature by attempted hydrogenation of **8i** using Lindlar catalysis, and only the starting material **8i** was recovered, as shown in Scheme 4.

3. Antibacterial activity

The antibacterial activity of the samples was assessed against a panel of erythromycin-susceptible and clinical erythromycin-resistant isolates, including *Staphylococcus aureus*, *Staphylococcus*



Scheme 2. Synthesis of the ketolide **10k**. (a) 10% Pd–C, HCOOH, $HCOONH_4$, H_2, 65 °C, 24 h, MeOH. **9k**, **10k**: Ar=3-quinolyl.



Scheme 3. Synthesis of the ketolide **10i**. (a) 10% Pd–C, HCOOH, $HCOONH_4$, H_2, 65 °C, 24 h, MeOH. **8i** , **10i**: Ar=4-isoquinolyl.

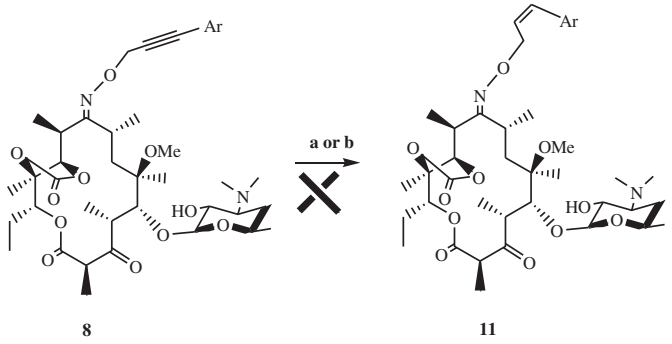
haemolyticus, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *S. pneumoniae*, *Streptococcus pyogenes*, and *Streptococcus dysgalactiae*. All isolates tested were identified by 16S rDNA sequencing. *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619 were used as controls. All the strains, separately labeled by corresponding genotypes and phenotypes, are listed in Table 1.

Azithromycin and clarithromycin were tested as the reference compounds. Data are presented in Table 2 as the minimal inhibitory concentration (MIC), which was determined by the broth microdilution method as recommended by the Clinical and Laboratory Standards Institute [31]

4. Results and discussion

Compounds **8**, bearing a 3-aryl-2-propargyl group at the 9-oxime, were equally as active as clarithromycin and azithromycin against erythromycin-susceptible strains, and showed significantly improved antibacterial activity against erythromycin-resistant bacteria as compared to the references. More importantly, some compounds, exemplified by **8h** and **8i**, even exhibited higher potency than previously reported **9k** bearing a 3-aryl-*E*-prop-2-enyl group at the 9-oxime [27]

The potency of series **8** was found to depend markedly on the aryl groups attached to the end of the propargyl linker. Among them, **8g** (5-indolyl) showed the poorest activity and was the only one that contained a potential hydrogen bond donor. Except for **8g**, the other sulfur-containing and nitrogen-containing compounds (**8a**–**8f**, **8h**–**8l**) were potential hydrogen bond acceptors. Nam reported the 2-thienyl group linked to a ketolide via a propenyl linker conferred high potency [25], but the compounds with a 2-thienyl group attached to the end of a propargyl group, such as **8a** (2-thienyl), **8e** (2-[5-(2-pyridyl)]thienyl), and **8f** (2-[5-(1-benzoyl)]



Scheme 4. Unsuccessful synthesis of the ketolide **11i**; only the starting material **8i** was recovered in the presence of the conditions a or b. (a) Lindlar catalyst (5% Pd on calcium carbonate poisoned with lead), H_2, 30 °C, 24 h, MeOH; (b) Lindlar catalyst, HCOOH, $HCOONH_4$, H_2, 35 °C, 24 h, MeOH. **8i** , **11i**: Ar=4-isoquinolyl.

Table 1
Selected organisms and their resistant determinants.

Strain		Phenotype	Genotype
Streptococcus pneumoniae	ATCC 49619	Erythromycin-susceptible	None
Streptococcus pneumoniae	PU 11	MLS-resistant(constitutive), PRSP[a]	*erm* + *mef*
Streptococcus pneumoniae	PU 09	Efflux, PSSP[b]	*mef*
Streptococcus pneumoniae	PU 27	MLS-resistant(constitutive), PSSP	*erm*
Streptococcus dysgalactiae	A 1	Efflux, erythromycin-resistant	NT[h]
Streptococcus pyogenes	A 2	MLS-resistant(constitutive)	NT
Streptococcus pyogenes	A 3	Erythromycin-susceptible	NT
Staphylococcus aureus	ATCC 29213	Erythromycin-susceptible	None
Staphylococcus aureus	PU 32	MLS-resistant(inducible), MRSA[c]	*ermA*
Staphylococcus aureus	PU 20	MLS-resistant(constitutive), MRSA	*ermC*
Staphylococcus aureus	PU 64	MLS-resistant(inducible), MSSA[d]	*ermA*
Staphylococcus haemolyticus	PU 19	MLS-resistant(constitutive), MRSCon[e]	*ermA*
Staphylococcus epidermidis	E 1	MLS-resistant(inducible), MSSE[f]	NT
Staphylococcus epidermidis	E 2	MLS-resistant(constitutive), MRSE[g]	NT
Staphylococcus hominis	E 3	MLS-resistant(inducible), MRSCon	NT

[a] PRSP: penicillin-resistant *Streptococcus pneumoniae*.
[b] PSSP: penicillin-susceptible *Streptococcus pneumoniae*.
[c] MRSA: methicillin-resistant *Staphylococcus aureus*.
[d] MSSA: methicillin-susceptible *Staphylococcus aureus*.
[e] MRSCon: methicillin-resistant *coagulase-negative Staphylococci*.
[f] MSSE: methicillin-susceptible *Staphylococcus epidermidis*.
[g] MRSE: methicillin-resistant *Staphylococcus epidermidis*.
[h] NT: not tested.

thienyl), were inferior to the other pyridine-containing and quinoline-containing compounds, such as **8b**–**8d**, **8h**–**8l**. This point strongly suggested nitrogen-containing heteroaryl groups are favorable due to their hydrogen bonding with bacterial rRNA. Within the fused bicyclic aryl groups, the point of attachment of the quinoline ring had an impact on antibacterial activity. For instance, **8i** (4-isoquinolyl) was significantly more potent than its analogs **8h** (5-isoquinolyl), whereas **8l** (6-quinolyl) was slightly more effective than its isomers **8k** (3-quinolyl) and **8j** (4-quinolyl). It is worth noting that the shift of the nitrogen atom from the aryl position-1 (**8j**) to the position-2 (**8i**) resulted in a dramatic improvement in antibacterial activity ranging from 4-fold to 32-fold against both inducibly MLS_B-resistant and efflux-resistant organisms, which suggests the existence of a powerful interaction between the latter and the bacterial rRNA. In contrast, within the monocyclic aryl groups, a shift of the nitrogen atom (**8b** vs **8c**) and incorporation of an additional nitrogen atom in the aryl groups (**8c** vs **8d**) led to less profound change in antibacterial activity.

Apart from the aryl groups, the nature of the side chain determined the potency of the 9-oxime ether ketolides. The loss of rigidity of the linker attenuated the activity (**8k** > **10k**; **8i** > **10i**), which revealed that greater flexibility might be unfavorable for formation of the optimal pharmacophoric conformation. Different linker chains resulted in different antibacterial profiles. For instance, **8i** was more effective than **9i** and **10i** (Ar=4-isoquinolyl), whereas **9k** was superior to **8k** and **10k** (Ar=3-quinolyl).

To our surprise, the SAR of series **8** differed greatly from the analogs **9** bearing 3-aryl-*E*-prop-2-enyl groups at the 9-oxime [27]. Isoquinolyl groups [**8h** (5-isoquinolyl) and **8i** (4-isoquinolyl)]

Table 2
In vitro antibacterial activity of ketolides against erythromycin-susceptible and-resistant pathogens.

Compd	MIC(μg/ml)														
	Streptococcus							*Staphylococcus*							
	S. pneumoniae				*S. dysgalactiae*	*S. pyogenes*		*S. aureus*				*S.haemolyticus*	*S. epidermidis*		*S.hominis*
	49619 eryS [a]	**PU 11 cMLS**	**PU 09 efflux**	**PU 27 cMLS**	**A 1 efflux**	**A 2 cMLS**	**A 3 eryS**	**29213 eryS**	**PU 32 iMLS**[b]	**PU 20 cMLS**[c]	**PU 64 iMLS**	**PU 19 cMLS**	**E 1 iMLS**	**E 2 cMLS**	**E 3 iMLS**
Cla [d]	0.032	>256	4	1	8	>256	0.032	0.25	1	>256	2	>256	>256	>256	>256
Azi [e]	0.25	>256	8	64	32	>256	0.125	1	8	>256	8	>256	>256	>256	>256
8a	0.25	64	1	4	1	32	0.25	1	1	NT[f]	NT	64	1	64	1
8b	≤0.008	128	0.25	0.5	0.064	128	≤0.008	0.064	0.125	NT	NT	>256	0.125	>256	0.125
8c	≤0.008	128	0.25	0.25	0.125	64	≤0.008	0.064	0.125	NT	NT	>256	0.125	256	0.125
8d	0.032	128	0.25	0.25	0.125	128	0.016	0.125	0.125	256	0.064	256	0.064	>256	0.064
8e	≤0.008	32	2	0.25	2	32	0.125	1	1	NT	NT	NT	4	128	8
8f	0.125	64	2	1	2	32	0.064	2	2	NT	NT	128	2	128	2
8g	0.5	128	2	4	2	128	0.5	1	2	NT	NT	NT	2	>256	8
8h	0.016	32	0.125	0.125	0.125	32	≤0.008	0.064	0.125	NT	NT	64	0.064	64	0.125
8i	≤0.008	16	0.032	0.064	0.016	16	≤0.008	0.016	0.032	NT	NT	32	0.016	32	0.064
8j	0.016	32	0.5	1	0.25	32	0.016	0.5	0.5	NT	NT	64	0.25	64	0.25
8k	≤0.008	64	0.5	0.5	0.5	64	≤0.008	0.25	0.5	128	0.25	128	0.25	>256	0.25
8l	0.016	64	0.25	0.25	0.25	64	≤0.008	0.125	0.125	64	0.125	64	0.032	>256	0.125
9k	0.016	32	0.25	0.125	0.25	32	≤0.008	0.25	0.5	>256	0.064	>256	0.032	>256	0.064
10k	0.064	64	0.5	1	0.5	32	0.016	0.5	1	>256	1	>256	0.5	>256	2
10i	0.032	32	0.5	1	0.25	64	0.016	0.125	0.5	>256	0.25	>256	0.25	>256	0.5

[a] eryS: Erythromycin susceptible.
[b] iMLS: Inducibly MLS_B resistant.
[c] cMLS: Constitutively MLS_B resistant.
[d] Cla: Clarithromycin.
[e] Azi: Azithromycin.
[f] NT: Not tested.

significantly enhanced potency compared to the corresponding quinolyl groups [**8j** (4-quinolyl), **8k** (3-quinolyl), and **8l** (6-quinolyl)], which is contrary to the previous conclusion drawn on the **9** series. We previously disclosed that a bicyclic aryl group is beneficial to antibacterial activity in contrast to a monocyclic aryl group in the **9** series [27], however, no appreciable effect was observed in the comparison of **8a** (2-thienyl), **8e** (2-[5-(2-pyridyl)] thienyl), and **8f** (2-[5-(1-benzoyl)]thienyl). Likewise, no improvement was observed when comparing **8b** (2-pyridyl), **8c** (3-pyridyl) and **8d** (5-pyrimidyl) to **8j** (4-quinolyl), **8k** (3-quinolyl), and **8l** (6-quinolyl).

Compared to the second-generation erythromycins, **8i** was significantly more active against all of the pathogens tested, and reached >4000-fold as active as the references against both erythromycin-and methicillin-resistant *S. homins* E3, and even >16000-fold against inducibly MLS_B-resistant *S. epidermis* E1. It is notable that *ermA*-mediated resistant *S. aureus* PU32 was methicillin-resistant (MRSA); however, **8i** had an MIC of 0.032 μg/mL while azithromycin was inactive (MIC of 8 μg/mL). As for efflux-resistant strains, for instance *S. pneumoniae* PU09 encoding an *mef* gene and *S. dysgalactiae* A1, **8i** was 125-fold and 500-fold more active than clarithromycin, respectively. Surprisingly, **8i** was markedly potent against constitutively MLS_B-resistant *S. pneumoniae* PU27 encoding an *erm* gene (MIC of 0.064 μg/mL) as compared to clarithromycin (MIC of 1 μg/mL) and azithromycin (MIC of 64 μg/mL). Regarding the other constitutively MLS_B-resistant bacteria PU11, A2, PU19, and E2, **8i** showed >8-fold improvement over the references, but unfortunately it was still only weakly active (MICs of 16–32 μg/mL).

5. Molecular docking and molecular modeling

To gain insight into the binding mode of the potent compounds **8i** and **9k** with the ribosome, we performed molecular docking and energy minimization by using GOLD and AMBER, respectively. The starting conformation was the crystal structure of cethromycin extracted from its crystal complex with the 50S ribosomal subunit of *Deinococcus radiodurans* (PDB code: 1NWX).

It has been shown that the arylalkyl moiety of the ketolides confers an additional and critical interaction with bacterial ribosomal RNA, particularly with mutation or methylation on A2058 (*Escherichia coli* numbering, equal to A2041 in *D. radiodurans*). The extended heteroaryl groups of telithromycin and cethromycin are considered to bind to domain II of 23s rRNA [17,18,32]. The aryl groups substituted at the 9-oxime via an appropriate linker (six-atom length) reportedly extend to the same spatial position [23]. According to our docking results, the 9-*O*-(3-arylalkyl) oxime sidechains of **8i** and **9k** may bind to a different pocket from the arylalkyl group of cethromycin, as illustrated in Fig. 3 and Fig. 4. The aryl groups of **9k** and **8i** approached domain V of 23s rRNA.

On the other hand, the variation in the chemical structures in series **8** and **9** produces an important difference in the binding mode. Compound **9k** could form a hydrogen bond with the hydroxyl group of the pentose of G2044 (3.7 Å, Fig. 3). Compound **8i** might hydrogen bond with the oxygen atom of the phosphate of C2421 (3.1 Å, Fig. 3). In addition to the hydrogen bonding, an extra hydrophobic stacking effect was found between **8i** and the adenine group of A2045, which may account for the stronger potency of **8i** compared to that of **9k**.

The aforementioned discrepancy of SAR found in the series **8** and **9** can be attributed to the structural variation of the sidechains and the resulting change of orientation of the aryl groups. In other words, the binding pocket located in the bacterial ribosome could not accommodate the steric bulk of orientationally unsuitable bicyclic aryl groups appended to the macrolide core via a propargyl linker. When the orientation is suitable, such as in the most potent candidate **8i**, hydrogen bonding and hydrophobic interaction are the most important attractive forces between the aryl group of the drug and the rRNA of the bacteria, which is consistent with the previous conclusion drawn on the X-ray crystal structure of the complexity of ketolides and bacterial rRNA [17]. In addition, the presence of the two kinds of interactions is implied by the

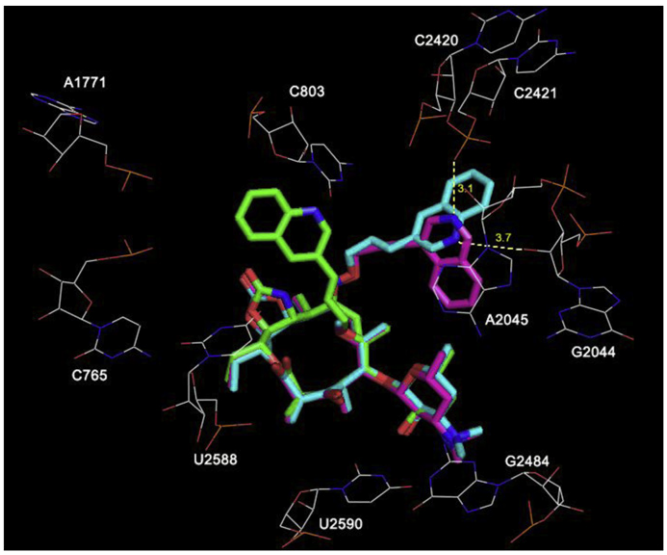


Fig. 3. The docking poses of **8i** (purple) and **9k** (cyan) overlapped with the crystal structure of cethromycin (green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

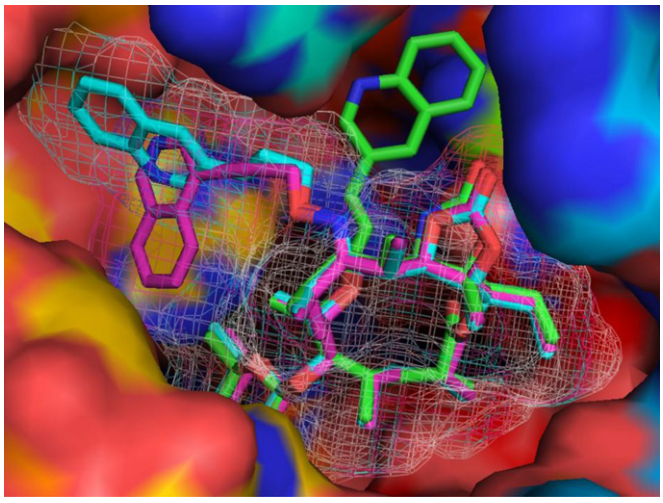


Fig. 4. The extended aryl groups of **8i** (purple), **9k** (cyan) and cethromycin (green) interact with different rRNA pockets. The surface of rRNA is shown in solid. The surfaces of **8i** and **9k** are shown in mesh. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

comparison of the potency of **8i** (4-isoquinolyl) and **8h** (5-isoquinolyl), as well as **8i** and **8c** (3-pyridyl). In conclusion, compound **8i** is more potent than the other two compounds because it can form both hydrogen bonds and hydrophobic interactions with bacterial ribosomal RNA.

6. Conclusion

A series of 9-*O*-(3-arylalkyl)oxime ketolides **8** and **10** containing a 11,12-cyclic carbonate was synthesized and evaluated. Ketolides **8** with a propargyl linker showed a very different profile of structure–activity relationships compared to previously reported ketolides **9** with a propenyl linker [27]. Without a rigid linker, the 9-*O*-(3-aryl-propgyl)oxime ketolides **10** were less potent than the corresponding series **8** and series **9**. Molecular docking studies elucidated the disparity of SAR found in the series **8** and **9**, and suggested the possibility of a novel binding mode that is different from teltithromycin and cethromycin.

It is interesting to note that **8** displayed significant antibacterial activity against inducibly MLS_B-resistant and efflux-mediated resistant pathogens, regardless of methicillin-susceptible or methicillin-resistant phenotypes carried. Among the compounds in the series **8**, **8h** (Ar=5-isoquinolyl) and **8i** (Ar=4-isoquinolyl) were the best candidates for further investigation.

7. Experimental

All solvents and reagents were obtained from commercial sources (J & K Scientific) and used without further purification unless otherwise noted. Flash column chromatography was performed on silica gel (0.035–0.070 mm, Aldrich). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on Bruker ARX 400 MHz and 600 MHz spectrometers with tetramethylsilane (TMS) as an internal standard. High resolution mass spectra (HRMS) were obtained with a Bruker Apex IV FT mass spectrometer.

7.1. Docking calculations

The crystal structure of the 50S ribosomal subunit in complex with cethromycin was retrieved from the RCSB Protein Data Bank (PDB code: 1NWX). Only residues within 30 Å of cethromycin were kept. The quinolinyl-propylene side chain in position 6 was removed and replaced with a methoxyl group. The carbamate nitrogen in position 11 was changed to oxygen. The carbonyl oxygen in position 9 was mutated to nitrogen and it was used as the anchor point for the oxime side chain. The docking calculation was performed using the GOLD 3.0.1 program. The oxime side of **8i** and **9k** was docked to the binding site through a covalent attachment with the oxime nitrogen. Each side chain was docked 10 times and the best docking solution according to the GoldScore fitness function was chosen as the binding conformation. The binding conformation was further optimized by energy minimization using Amber 9. The Parm99 force field was applied for the 50S ribosome, while the ligand parameters were taken from the general Amber force field (GAFF), and the atomic partial charges were calculated by the bcc method. The energy minimization consisted of 3000 steps in which the first 1000 were steepest descent (SD) and the last 2000 conjugate gradient (CG).

7.2. 3-O-Descladinosyl-3-OH-6-O-methylerythromycin A E-9-oxime (*2*)

Compound **1**, 2′,4″-bis(trimethylsilyl)-6-*O*-methylerythromycin A 9-*O*-(1-ethoxycyclohexyl)oxime, was prepared in three steps following a published procedure [28] starting from commercially available erythromycin A 9-oxime (20.00 g).

To a solution of resulting **1** in ethanol (30 mL) was added a dilute HCl (8 mL of 36% aqueous HCl in 80 mL of water). The mixture was stirred at 40 °C for 1 h, and then was adjusted to pH 9 with 25% aqueous NH_3. The precipitate was collected by filtration and washed with cold water. Recrystallization form ethanol–water afforded 10.40 g of **2** [27]. MS ($M + H^+$) *m/z*: 605.5.

7.3. 2′-O-acetyl-3-O-descladinosyl-3-OH-6-O-methylerythromycin A E-9-O-acetyloxime (*3*)

A solution of **2** (6.61 g, 10.93 mmol) in CH_2Cl_2 (50 mL) was treated with acetic anhydride (3.2 mL, 32.60 mmol) at room temperature for 1 h. The reaction mixture was washed with

saturated $NaHCO_3$, water and brine. The organic layer was concentrated and dried to get **3** [27] (6.90 g, 91.7%).

7.4. 2′-O-acetyl-3-O-descladinosyl-3-OH-6-O-methylerythromycin A E-9-O-propargyloxime (**4**)

To a solution of **3** (0.50 g, 0.73 mmol) in DMF (15 mL) was added KOtBu (0.12 g, 1.10 mmol). After stirring for 10 min, additional KOtBu (0.81 g, 0.73 mmol) and propargyl bromide (0.07 mL, 0.80 mmol) were added. The reaction mixture was stirred for 1 h at room temperature, then extracted with ethyl acetate, and washed with water and brine. The organic layer was concentrated and dried to yield **4** (0.47 g, 94.5%). **4**: HRMS (ESI) (MH^+) *m/z* 685.42599, calcd for $C_{35}H_{61}N_2O_{11}$ 685.42699. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.25 (dd, J = 1.6 H, 11.0 Hz, 1 H, H-13), 4.76 (dd, J = 7.7 Hz, 10.2 Hz, 1 H, H-2′), 4.62 (d, J = 7.6 Hz, 1 H, H-1′), 4.57 (s, 2 H, C**H**$_2$–C≡CH), 4.48 (s, 1 H, 11-OH), 3.81 (s, 1 H, H-11), 3.71 (d, J = 1.7 Hz, 1 H, H-5), 3.58–3.62 (m, 1 H, H-8), 3.47–3.51 (m, 1 H, H-5′), 3.41 (d, J = 10.5 Hz, 1 H, H-3), 3.33 (s, 1 H, 12-OH), 2.98 (s, 3 H, 6-OCH_3), 2.57–2.73 (m, 3 H, H-10, H-2, H-3′), 2.49 (t, J = 2.1 Hz, 1 H, CH_2–C≡C**H**), 2.26 (s, 6 H,–$N(CH_3)_2$), 2.06–2.11 (m, 1 H, H-4), 1.94–1.96 (m, 1 H, H-14eq), 2.06 (s, 3 H, 2′-*O*–Ac), 1.71–1.75 (m, 1 H, H-4′eq), 1.31–1.49 (m, 3 H, H-7, H-14ax), 1.30 (s, 3 H, 6-CH_3), 1.15–1.24 (m, 13 H, H-4′ax, 10-CH_3, 12-CH_3, 2′-CH_3, 5′-CH_3), 0.97 (d, J = 7.0 Hz, 3 H, 4-CH_3), 0.90 (d, J = 7.3 Hz, 3 H, 8-CH_3), 0.83 (t, 3 H, 15-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 170.8, 169.8, 99.5, 80.3, 79.7, 78.0, 77.2, 74.2, 73.8, 71.2 70.2, 68.4, 62.9, 60.7, 49.9, 44.0, 36.8, 35.8, 32.9, 30.8, 26.2, 21.3, 21.2, 20.9, 19.1, 18.2, 16.1, 15.2, 15.0, 10.2, 7.6.

7.5. 2′-O-acetyl-3-O-descladinosyl-3-OH-6-O-methylerythromycin A E-9-O-propargyloxime 11,12-cyclic carbonate (**5**)

To an ice-cold solution of **4** (1.77 g, 2.58 mmol) and pyridine (2.29 mL, 28.49 mmol) in CH_2Cl_2 (70 mL) was added dropwise a solution of bis(trichloromethyl)carbonate (1.54 g, 5.18 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at −5 °C for 4 h and then stirred at room temperature for 12 h. After the reaction mixture was allowed to cool to 0 °C, to the reaction mixture was added dropwise brine (70 mL). The organic layer was washed with saturated $NaHCO_3$, water and brine, and was concentrated to afford **5** (1.49 g, 81.4%).

7.6. 2′-O-acetyl-3-O-descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-propargyloxime 11,12-cyclic carbonate (**6**)

A solution of *N*-chlorosuccinimide (NCS) (0.45 g, 3.35 mmol) in CH_2Cl_2 (30 mL) was stirred at −15 °C for 10 min and then dimethyl sulfide (DMS) (0.29 mL, 3.98 mmol) was added slowly. After stirring for 30 min, a solution of **5** (1.49 g, 2.10 mmol) in CH_2Cl_2 (20 mL) was added to the reaction mixture. When TLC showed the reaction reached completion, triethylamine (0.58 mL) was added dropwise to the reaction mixture. The solution soon became clear and stirring was continued at −5 °C for 1 h. The organic layer was washed with saturated $NaHCO_3$, water and brine, and was concentrated to yield **6** (1.40 g, 94.3%). **6**: HRMS(ESI) (MH^+) *m/z* 709.38920, calcd for $C_{36}H_{57}N_2O_{12}$ 709.39060; ^{1}H NMR (600 MHz, $CDCl_3$) δ:, 5.04 (d, J = 10.2 Hz, 1 H, H-13), 4.79 (s, 1 H, H-11), 4.74 (t, J = 8.4 Hz, 1 H, H-2′), 4.65 and 4.61 (d, J = 15.6 Hz, 2 H, C**H**$_2$–C≡CH), 4.37 (d, J = 7.2 Hz, 1 H, H-1′), 4.17 (d, J = 7.2 Hz, 1 H, H-5), 3.82 (q, J = 6.0 Hz, 1 H, H-2), 3.62 (br, 1 H, H-8), 3.52–3.55 (m, 1 H, H-5′), 2.99–3.02 (m, 1 H, H-4), 2.70 (s, 3 H, 6-OCH_3), 2.65–2.70 (m, 1 H, H-3′), 2.52–2.53 (m, 1 H, H-10), 2.40 (s, 1 H, CH_2–C≡C**H**), 2.25 (s, 6 H, –N $(CH_3)_2$), 2.04 (s, 3 H, 2′-OAc), 1.89–1.93 (m, 1 H, H-14eq), 1.74 (d, 1 H), 1.56 (s, 3 H, 12-CH_3), 1.53–1.60 (m, 1 H, H-14ax), 1.38 (s, 3 H, 6-CH_3), 1.36 (d, J = 7.2 Hz, 3 H, 2-CH_3), 1.24–1.26 (m, 6 H, 10-CH_3, 5′-CH_3), 1.12 (d, J = 7.8 Hz, 3 H, 4-CH_3), 0.99 (d, J = 6.6 Hz, 3 H, 8-CH_3), 0.89 (t, J = 7.2 Hz, 3 H, 15-CH_3).

7.7. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(4′-isoquinolyl)-2-propargyl] oxime 11,12-cyclic carbonate (**8i**)

To a solution of **6** (1.000 g, 1.412 mmol), CuI (27 mg, 0.14 mmol) and $PdCl_2(PPh_3)_2$ (0.050 g, 0.05 mmol) in acetonitrile (12 mL) were added 4-bromoisoquinoline (0.734 g, 3.35 mmol) and triethylamine (0.29 mL, 2.12 mmol). The reaction mixture was flushed with nitrogen and sealed in a pressure tube. The reaction mixture was stirred at 80 °C for 3 h. The mixture was extracted with ethyl acetate and washed with water and brine. The organic phase was concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (15:0.4:0.1 $CH_2Cl_2/C_2H_5OH/NH_3\cdot H_2O$) to yield **7i** (0.278 g, 23.6%). **7i**: ^{1}H NMR (400 MHz, CDCl3) δ: [9.18 (s, 1 H), 8.65 (s, 1 H), 8.29 (d, J = 7.6 Hz, 1 H), 7.97 (d, J = 7.6 Hz, 1 H), 7.79 (t, J = 6.4 Hz, 1 H), 7.65 (t, J = 6.4 Hz, 1 H), 4-isoquinolyl], 4.97–5.05 (m, 3 H, C**H**$_2$–C≡C–Ar, H-13), 4.66–4.85 (m, 2 H, H-11, H-2′), 4.38 (d, J = 6.4 Hz, 1 H, H-1′), 4.15 (d, J = 6.8 Hz, 1 H, H-5), 3.55–3.78 (m, 3 H, H-8, H-2, H-5′), 3.00–3.11 (m, 1 H, H-4), 2.67 (s, 3 H, 6-OCH_3), 2.50–2.55 (m, 2 H, H-10, H-3′), 2.33 (s, 6H, –$N(CH_3)_2$), 2.09 (s, 3 H, 2′-$OCCH_3$), 1.80–1.92 (m, 2 H, H-4′eq, H-14eq), 1.57 (s, 3 H, 12-CH_3), 1.43 (s, 3 H, 6-CH_3), 1.25–1.34 (m, 9 H, 10-CH_3, 5′-CH_3, 2-CH_3), 1.11 (d, J = 6.8 Hz, 3 H, 4-CH_3), 1.02 (d, J = 5.6 Hz, 3 H, 8-CH_3), 0.89 (t, 3 H, 15-CH_3).

A solution of **7i** (0.278 g, 0.333 mmol) in MeOH (25 mL) was stirred at 65 °C for 3 h and was then concentrated. The residue was purified by column chromatography on silica gel (5:5:0.2 petroleum ether/acetone/triethylamine) to yield analytically pure product **8i** (0.126 g, 47.7%). **8i**: HRMS (ESI) (MH^+) *m/z* 794.42221, calcd for $C_{43}H_{60}N_3O_{11}$ 794.42224. ^{1}H NMR (400 MHz, $CDCl_3$) δ: [9.18 (s, 1 H), 8.65 (s, 1 H), 8.30 (d, J = 8.4 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 1 H), 7.79 (td, 1 H), 7.64 (td, 1 H), 4-isoquinolyl], 4.97–5.06 (m, 3 H, C**H**$_2$–C≡C–Ar, H-13), 4.82 (s, 1 H, H-11), 4.28 (d, J = 7.3 Hz, 1 H, H-1′), 4.17 (d, J = 8.5 Hz, 1 H, H-5), 3.78 (br, 1 H, H-8), 3.46–3.55 (m, 2 H, H-2, H-5′), 3.18 (dd, J = 7.3 and 10.2 Hz, 1 H, H-2′), 3.01–3.05 (m, 1 H, H-4), 2.69 (s, 3 H, 6-OCH_3), 2.63 (br, 1 H, H-10), 2.40–2.47 (m, 1 H, H-3′), 2.26 (s, 6 H, –$N(CH_3)_2$), 1.89–1.93 (m, 1 H, H-14eq), 1.64–1.75 (m, 3 H, H-7, H-4′eq), 1.57 (s, 3 H, 12-CH_3), 1.46 (s, 3 H, 6-CH_3), 1.21–1.33 (m, 12 H, 4-CH_3, 10-CH_3, 5′-CH_3, 2-CH_3), 1.02 (d, J = 6.8 Hz, 3 H, 8-CH_3), 0.89 (t, J = 7.2 Hz, 3 H, 15-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.9, 169.0, 165.9, 154.4, 152.1, 146.6, 135.8, 131.2, 127.9, 127.7, 125.2, 115.5, 103.9, 93.2, 84.7, 82.7, 80.9, 79.4, 78.5, 77.2, 76.4, 70.4, 69.5, 65.9, 62.0, 51.1, 49.7, 47.8, 46.1, 40.2, 38.4, 28.2, 22.5, 21.2, 19.8, 18.9, 15.8, 15.5, 14.3, 13.2, 10.4.

7.8. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(2′-thienyl)-2-propargyl] oxime 11,12-cyclic carbonate (**8a**)

Following the procedure for the synthesis **7i** and **8i**, **7a** and **8a** were obtained from the coupling of **6** (0.700 g, 0.988 mmol) and 2-bromothiophene (0.28 mL, 2.96 mmol) in yields of 15.0% and 64.2%, respectively. **8a**: HRMS(ESI) (MH^+) *m/z*: 749.36901, calcd for $C_{38}H_{57}N_2O_{11}S$ 749.36776; ^{1}H NMR (400 MHz, $CDCl_3$) δ: [7.22 (d, J = 4.4 Hz, 1 H), 7.18 (d, J = 3.6 Hz, 1 H), 6.93–6.95 (m, 1 H), 2-thienyl], 5.02 (dd, J = 2.4 Hz, 10.0 Hz,1 H, H-13), 4.90 and 4.84 (d, J = 16.0 Hz, 2 H, C**H**$_2$–C≡C–Ar), 4.77 (s, 1 H, H-11), 4.30 (d, J = 7.2 Hz, 1 H, H-1′), 4.16 (d, J = 8.4 Hz, 1 H, H-5), 3.51–3.80 (m, 3 H, H-8, H-5′, H-2), 3.25 (dd, J = 7.2 Hz, 10.0 Hz, 1 H, H-2′), 3.01–3.05 (m, 1 H, H-4), 2.71 (s, 3 H, 6-OCH_3), 2.49–2.64 (m, 2 H, H-3′, H-10), 2.37 (s, 6 H, –N $(CH_3)_2$), 1.87–1.91 (m, 1 H, H-14eq), 1.67–1.77 (m, 2 H, H-7, H-4′eq), 1.56 (s, 3 H, 12-CH_3), 1.41 (s, 3 H, 6-CH_3), 1.33 (d, J = 6.8 Hz, 3 H, 2-CH_3), 1.23–1.26 (m, 10 H, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 1.00 (d, J = 6.4 Hz, 3 H, 8-CH_3), 0.88 (t, J = 7.6 Hz, 3 H, 15-CH_3); ^{13}C NMR

(75 MHz, $CDCl_3$) δ: 204.2, 169.2, 165.9, 154.5133.4, 132.4, 131.9, 127.3, 127.0, 103.7, 89.9, 84.9, 82.8, 79.6, 79.3, 78.6, 70.4, 69.3, 66.3, 62.3, 51.3, 49.9, 48.0, 40.4, 38.6, 31.0, 29.1, 26.7, 22.7, 21.2, 19.9, 19.0, 16.0, 15.6, 14.5, 13.4, 10.5.

7.9. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(2′-pyridyl)-2-propargyl] oxime 11,12-cyclic carbonate (**8b**)

Following the procedure for the synthesis **7i** and **8i**, **7b** and **8b** were obtained from the coupling of **6** (0.700 g, 0.988 mmol) and 2-bromopyridine (0.29 mL, 2.96 mmol) in yields of 14.2% and 66.4%, respectively. **8b**: HRMS(ESI) (MH^+) *m/z*: 744.40835, calcd for $C_{39}H_{58}N_3O_{11}$ 744.40659; ^{1}H NMR (400 MHz, $CDCl_3$) δ: [8.52 (d, *J* = 4.8 Hz, 1 H), 7.59–7.63 (m, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.19 (dd, *J* = 6.8 Hz, 5.2 Hz, 1 H), 2-pyridyl], 5.00 (dd, *J* = 10.0 Hz, 2.0 Hz,1 H, H-13), 4.89 and 4.83 (d, *J* = 16.0 Hz, 2 H, CH_2–C≡C–Ar), 4.77 (s, 1 H, H-11), 4.26 (d, *J* = 7.2 Hz, 1 H, H-1′), 4.15 (d, *J* = 8.4 Hz, 1 H, H-5), 3.79 (q, *J* = 6.8 Hz, 1 H, H-2), 3.64 (br, 1 H, H-8), 3.47–3.53 (m, 1 H, H-5′), 3.17 (dd, *J* = 10.0 Hz, 7.2 Hz, 1 H, H-2′), 2.95–3.07 (m, 1 H, H-4), 2.68(s, 3 H, 6-OCH_3), 2.41–2.52 (m, 2 H, H-10, H-3′), 2.26 (s, 6 H, -N $(CH_3)_2$), 1.85–1.91 (m, 1 H, H-14eq), 1.64–1.69 (m, 2 H, H-7, H-4′eq), 1.53 (s, 3 H, 12-CH_3), 1.40 (s, 3 H, 6-CH_3), 1.35(d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.20–1.24 (m, 10 H, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 0.97 (d, *J* = 6.8 Hz, 3 H, 8-CH_3), 0.86 (t, 3 H, *J* = 7.2 Hz, 15-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.0, 169.2, 165.8, 154.5, 150.0, 143.1, 136.2, 132.1, 127.4, 123.0, 103.8, 85.8, 85.2, 84.8, 82.8, 79.6, 78.5, 76.4, 70.4, 69.5, 66.0, 61.9, 51.2, 49.8, 48.0, 40.3, 38.4, 28.5, 26.5, 22.5, 21.2, 19.9, 18.9, 16.0, 15.5, 14.4, 13.3, 10.5.

7.10. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(3′-pyridyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8c**)

Following the procedure for the synthesis **7i** and **8i**, **7c** and **8c** were obtained from the coupling of **6** (1.000 g, 1.41 mmol) and 3-bromopyridine (0.41 mL, 4.20 mmol) in yields of 10.1% and 46.9%, respectively. **8c**: HRMS(ESI) (MH^+) *m/z* 744.40750, calcd for $C_{39}H_{58}N_3O_{11}$ 744.40659; ^{1}H NMR (400 MHz, $CDCl_3$) δ: [8.65 (s, 1 H), 8.53 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H),7.24–7.26 (m, 1 H), 3-pyridyl], 5.04 (dd, *J* = 2.4 Hz, 10.4 Hz, 1 H, H-13), 4.91 and 4.85 (d, *J* = 15.6 Hz, 2 H, C**H**$_2$–C≡C–Ar), 4.80 (s, 1 H, H-11), 4.30 (d, *J* = 7.2 Hz, 1 H, H-1′), 4.19 (d, *J* = 8.4 Hz, 1 H, H-5), 3.81 (q, *J* = 6.8 Hz, 1 H, H-2), 3.66 (br, 1 H, H-8), 3.53–3.57 (m, 1 H, H-5′), 3.22 (t, *J* = 7.6 Hz, 1 H, H-2′), 3.02–3.06 (m, 1 H, H-4), 2.72 (s, 3 H, 6-OCH_3), 2.47–2.56 (m, 2 H, H-3′, H-10), 2.30 (s, 6 H, -N $(CH_3)_2$), 1.89–1.94 (m, 1 H, H-14eq), 1.69–1.72 (m, 2 H, H-7, H-4′eq), 1.56 (s, 3 H, 12-CH_3), 1.44 (s, 3 H, 6-CH_3), 1.36 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.20–1.31 (m, 10 H, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 1.01 (d, *J* = 6.8 Hz, 3 H, 8-CH_3), 0.90 (t, 3 H, *J* = 7.2 Hz, 15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.1, 169.2, 165.9, 154.5, 152.5, 148.8, 138.8, 103.8, 89.3, 84.9, 82.8, 79.5, 78.6, 77.4, 76.6, 70.4, 69.4, 66.2, 62.0, 51.3, 49.8, 47.9, 40.4, 38.5, 28.8, 26.6, 22.6, 21.3, 19.9, 19.0, 15.9, 15.6, 14.4, 13.4, 10.5.

7.11. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(5′-pyrimidyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8d**)

Following the procedure for the synthesis **7i** and **8i**, **7d** and **8d** were obtained from the coupling of **6** (0.700 g, 0.988 mmol) and 5-bromopyrimidine (0.471 g, 2.96 mmol) in yields of 37.3% and 14.6%, respectively. **8d**: HRMS (ESI) (MH^+) *m/z* 745.40115, calcd for $C_{38}H_{57}N_4O_{11}$ 745.40184; ^{1}H NMR (400 MHz, $CDCl_3$) δ: [9.10 (s, 1 H), 8.73 (s, 2 H), 5-pyrimidyl], 5.01 (dd, *J* = 2.4 Hz, 10.4 Hz,1 H, H-13), 4.88 and 4.83 (d, *J* = 16.4 Hz, 2 H, CH_2–C≡C–Ar), 4.76 (s, 1 H, H-11), 4.28 (d, *J* = 7.6 Hz, 1 H, H-1′), 4.17 (d, *J* = 8.4 Hz, 1 H, H-5), 3.80 (q, *J* = 6.8 Hz, 1 H, H-2), 3.50–3.64 (m, 2 H, H-5′, H-8), 3.19 (dd, *J* = 7.6 Hz, 10.0 Hz, 1 H, H-2′), 2.98–3.02 (m, 1 H, H-4), 2.68 (s, 3 H, 6-OCH_3), 2.47–2.53 (m, 2 H, H-3′, H-10), 2.29 (s, 6 H, –N $(CH_3)_2$), 1.85–1.90 (m, 1 H, H-14eq), 1.66–1.69 (m, 2 H, H-7, H-4′eq), 1.53(s, 3 H, 12-CH_3), 1.40 (s, 3 H, 6-CH_3), 1.33 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.21–1.32 (m, 10 H, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 0.98 (d, *J* = 6.8 Hz, 3 H, 8-CH_3), 0.87 (t, *J* = 7.2 Hz, 3 H, 15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.0, 169.2, 166.2, 158.9, 157.0, 154.5, 119.5, 103.8, 93.2, 84.8, 82.8, 79.4, 79.2, 78.5, 76.5, 70.4, 69.5, 66.2, 61.8, 51.2, 49.8, 47.8, 40.4, 38.4, 31.0, 28.7, 26.6, 22.6, 21.2, 19.9, 18.9, 15.8, 15.6, 14.4, 13.3, 10.4.

7.12. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-[2′-(5′-(2"-pyridyl))thienyl]-2-propargyl]oxime 11,12-cyclic carbonate (**8e**)

Following the procedure for the synthesis **7i** and **8i**, **7e** and **8e** were obtained from the coupling of **6** (0.700 g, 0.988 mmol) and 2-(5-bromo-2-thienyl)pyridine (0.505 g, 2.10 mmol) in yields of 6.9% and 48.5%, respectively. **8e**: HRMS(ESI)(MH^+) *m/z*: 826.39418, calcd for $C_{43}H_{60}N_3O_{11}S$ 826.39431; ^{1}H NMR (600 MHz, $CDCl_3$) δ: [8.54 (d, *J* = 4.2 Hz, 1 H), 7.65–7.69 (m, 1 H), 7.61(d, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 3.6 Hz, 1 H), 7.15–7.20(m, 2 H), 2-(5-(2-pyridyl)thienyl)], 5.04 (d, *J* = 9.0 Hz, 1 H, H-13), 4.93 and 4.88 (d, *J* = 15.6 Hz, 2 H, C**H**$_2$–C≡C–Ar), 4.79 (s, 1 H, H-11), 4.32 (d, *J* = 7.2 Hz, 1 H, H-1′), 4.17 (d, *J* = 6.6 Hz, 1 H, H-5), 3.54–3.82 (m, 3 H, H-8, H-5′, H-2), 3.26 (dd, *J* = 7.8 Hz, 9.6 Hz, 1 H, H-2′), 3.03–3.06 (m, 1 H, H-4), 2.73 (s, 3 H, 6-OCH_3), 2.61–2.70 (m, 2 H, H-3′, H-10), 2.39 (s, 6 H, –N $(CH_3)_2$), 1.89–1.93 (m, 1 H, H-14eq), 1.76 (d, *J* = 12.0 Hz, 1 H, H-7), 1.68–1.72 (m, 1 H, H-4′eq), 1.57 (s, 3 H, 12-CH_3), 1.42 (s, 3 H, 6-CH_3), 1.33 (d, *J* = 4.8 Hz, 3 H, 2-CH_3), 1.24–1.36 (m, 10 H, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 1.02 (d, *J* = 3.6 Hz, 3 H, 8-CH_3), 0.89 (t, *J* = 7.2 Hz, 3 H, 15-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.8, 168.6, 165.7, 154.2, 151.6, 149.4, 136.4, 133.2, 132.8, 124.2, 123.9, 122.0, 118.6, 69.9, 68.9, 65.9, 62.0, 50.9, 49.5, 47.6, 40.0, 20.9, 15.2, 14.1, 10.2.

7.13. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(2′-(5′-benzoyl)thienyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8f**)

Following the procedure for the synthesis **7i** and **8i**, **7f** and **8f** were obtained from the coupling of **6** (0.600 g, 0.847 mmol) and 2-bromo-5-benzoylthiophene (0.452 g, 1.69 mmol) in yields of 26.7% and 23.9%, respectively. **8f**: HRMS(ESI) (MH^+) *m/z* 853.39585, calcd for $C_{45}H_{61}N_2O_{12}S$ 853.39397; ^{1}H NMR (600 MHz, $CDCl_3$) δ: [7.83–7.85 (m, 2 H), 7.58–7.61 (m, 1 H), 7.49–7.52 (m, 3 H), 7.19 (d, *J* = 3.6 Hz, 1 H), 2-(5-benzoyl)thienyl], 5.04 (dd, *J* = 3.0 Hz, 7.2 Hz,1 H, H-13), 4.92 and 4.88 (d, *J* = 16.2 Hz, 2 H, C**H**$_2$–C≡C–Ar), 4.80 (s, 1 H, H-11), 4.30 (d, *J* = 7.8 Hz, 1 H, H-1′), 4.19 (d, *J* = 9.0 Hz, 1 H, H-5), 3.81 (q, 1 H, H-2), 3.65 (br, 1 H, H-8), 3.53–3.56 (m, 1 H, H-5′), 3.20 (dd, *J* = 7.8 Hz, 10.2 Hz, 1 H, H-2′), 3.03–3.05 (m, 1 H, H-4), 2.72 (s, 3 H, 6-OCH_3), 2.47–2.54 (m, 2 H, H-3′, H-10), 2.29 (s, 6 H, –N $(CH_3)_2$), 1.89–1.93 (m, 1 H, H-14eq), 1.68–1.72 (m, 2 H, H-7, H-4′eq), 1.56 (s, 3 H, 12-CH_3), 1.43 (s, 3 H, 6-CH_3), 1.35 (d, *J* = 7.2 Hz, 3 H, 2-CH_3), 1.23–1.27 (m, 10 H, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 1.02 (d, *J* = 6.6 Hz, 3 H, 8-CH_3), 0.89 (t, *J* = 7.2 Hz, 3 H, 15-CH_3).

7.14. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(5′-indolyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8g**)

Following the procedure for the synthesis **7i** and **8i**, **7g** and **8g** were obtained from the coupling of **6** (0.600 g, 0.847 mmol) and 5-bromoindole (0.415 g, 2.12 mmol) in yields of 7.9% and 40.3%, respectively. **8g**: HRMS(ESI) (MH^+) *m/z*: 782.42287, calcd for $C_{42}H_{60}N_3O_{11}$ 782.42224; ^{1}H NMR (600 MHz, $CDCl_3$) δ: [8.33 (s, 1 H), 7.75 (s, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.25 (d, 1 H), 7.22 (d, *J* = 2.4 Hz, 1H), 6.51 (s, 1 H), 5-indolyl], 5.03 (dd, 1 H, H-13), 4.92 and 4.87

(d, J = 16.0 Hz, 2 H, C**H**$_2$–C≡C–Ar), 4.78 (br, 1 H, H-11), 4.30 (d, J = 7.2 Hz, 1 H, H-1′), 4.15 (br, 1 H, H-5), 3.52–3.84 (m, 3 H, H-8, H-5′, H-2), 3.26 (dd, J = 7.2 Hz, 9.6 Hz, 1 H, H-2′), 3.02–3.04 (m, 1 H, H-4), 2.73 (s, 3 H, 6-OCH$_3$), 2.49–2.61 (m, 2 H, H-3′, H-10), 2.35 (s, 6 H, –N(CH$_3$)$_2$), 1.71–1.93 (m, 3 H, H-14eq, H-7, H-4′eq), 1.59 (s, 3 H, 12-CH$_3$), 1.42 (s, 3 H, 6-CH$_3$), 1.33 (d, J = 6.8 Hz, 3 H, 2-CH$_3$), 1.24–1.36 (m, 10 H, 4-CH$_3$, 10-CH$_3$, 5′-CH$_3$, H-4′ax), 1.03 (d, J = 3.6 Hz, 3 H, 8-CH$_3$), 0.89 (t, J = 7.2 Hz, 3 H, 15-CH$_3$).

7.15. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(5′-isoquinolyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8h**)

Following the procedure for the synthesis **7i** and **8i**, **7h** and **8h** were obtained from the coupling of **6** (0.700 g, 0.988 mmol) and 5-bromoisoquinoline (0.514 g, 2.47 mmol) in yields of 13.5% and 28.6%, respectively. **8h**: HRMS(ESI) (MH$^+$) m/z: 794.42208, calcd for $C_{43}H_{60}N_3O_{11}$ 794.42224; ^{1}H NMR (400 MHz, CDCl$_3$) δ: [9.25 (s, 1 H), 8.61 (s, 1 H), 8.11 (d, J = 4.0 Hz, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.55 (t, J = 4.0 Hz,1 H), 5-isoquinolyl], 4.96–5.05 (m, 3 H, C**H**$_2$–C≡C–Ar, H-13),, 4.82 (s, 1 H, H-11), 4.29 (d, J = 4.0 Hz, 1 H, H-1′), 4.17 (d, J = 8.0 Hz, 1 H, H-5), 3.54–3.80 (m, 3 H, H-2, H-5′, H-8), 3.23 (t, J = 8.0 Hz, 1 H, H-2′), 3.02–3.04 (m, 1 H, H-4), 2.69 (s, 3 H, 6-OCH$_3$), 2.55–2.57 (m, 2 H, H-3′, H-10), 2.33 (s, 6 H, –N(CH$_3$)$_2$), 1.89–1.91 (m, 1 H, H-14eq), 1.69–1.72 (m, 2 H, H-7, H-4′eq), 1.57 (s, 3 H, 12-CH$_3$), 1.47 (s, 3 H, 6-CH$_3$), 1.22–1.38 (m, 12 H, 4-CH$_3$, 10-CH$_3$, 5′-CH$_3$, 2-CH$_3$), 1.02 (d, J = 4.0 Hz, 3 H, 8-CH$_3$), 0.89 (t, J = 8.0 Hz, 3 H, 15-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 204.1, 169.1, 166.0, 154.6, 152.7, 144.1, 136.3, 134.4, 128.2, 126.8, 120.0, 119.0, 103.7, 92.0, 84.8, 82.9, 82.5, 79.5, 78.5, 76.5, 70.3, 69.3, 66.2, 62.2, 51.2, 49.8, 47.9, 40.4, 38.5, 28.9, 26.6, 22.6, 21.2, 19.9, 19.0, 16.0, 15.7, 14.4, 13.4, 10.5.

7.16. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(4′-quinolyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8j**)

Following the procedure for the synthesis **7i** and **8i**, **7j** and **8j** were obtained from the coupling of **6** (0.600 g, 0.847 mmol) and 4-bromoquinoline (0.400 g, 2.12 mmol) in yields of 15.0% and 33.1%, respectively. **8j**: HRMS(ESI) (MH$^+$) m/z 794.42359, calcd for $C_{43}H_{60}N_3O_{11}$ 794.42224; ^{1}H NMR (600 MHz, CDCl$_3$) δ: [8.85 (d, J = 4.2 Hz, 1 H), 8.30 (d, J = 8.4 Hz, 1 H), 8.09 (d, J = 9.0 Hz, 1 H), 7.73 (t, J = 7.2 Hz, 1 H), 7.61 (t, J = 7.2 Hz, 1 H), 7.46 (d, J = 4.2 Hz, 1 H), 4-quinolyl], 4.98–5.06 (m, 3 H, H-13, C**H**$_2$–C≡C–Ar), 4.82 (s, 1 H, H-11), 4.29 (d, J = 7.2 Hz, 1 H, H-1′), 4.19 (d, J = 8.4 Hz, 1 H, H-5), 3.71–3.81 (m, 2 H, H-8, H-2), 3.52–3.55 (m, 1 H, H-5′), 3.19 (dd, J = 7.8 Hz, 10.2 Hz, 1 H, H-2′), 3.01–3.05 (m, 1 H, H-4), 2.71 (s, 3 H, 6-OCH$_3$), 2.58 (br, 1 H, H-10), 2.43–2.49 (m, 1 H, H-3′), 2.28 (s, 6 H, –N(CH$_3$)$_2$), 1.89–1.94 (m, 1 H, H-14eq), 1.72 (d, J = 13.8 Hz, 1 H, H-7), 1.67 (d, J = 12.0 Hz, 1 H, H-4′eq), 1.57 (s, 3 H, 12-CH$_3$), 1.55–1.62 (m, 1 H, H-14ax), 1.47 (s, 3 H, 6-CH$_3$), 1.34 (d, J = 6.0 Hz, 3 H, 2-CH$_3$), 1.22–1.30 (m, 10 H, 4-CH$_3$, 10-CH$_3$, 5′-CH$_3$, H-4′ax), 1.03 (d, J = 6.6 Hz, 3 H, 8-CH$_3$), 0.89 (t, J = 7.2 Hz, 3 H, 15-CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 204.1, 169.2, 166.3, 154.5, 149.8, 148.2, 130.0, 129.9, 129.5, 128.0, 127.4, 126.2, 123.9, 103.9, 95.5, 84.8, 82.9, 81.8, 79.5, 78.6, 70.4, 69.5, 66.2, 62.1, 51.3, 49.9, 47.9, 40.4, 38.5, 29.8, 28.7, 26.7, 22.6, 21.3, 20.0, 19.0, 15.9, 15.7, 14.4, 13.4, 10.5.

7.17. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(3′-quinolyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8k**)

Following the procedure for the synthesis **7i** and **8i**, **7k** and **8k** were obtained from the coupling of **6** (0.700 g, 0.988 mmol) and 3-bromoquinoline (0.342 mL, 2.51 mmol) in yields of 11.6% and 41.7%, respectively. **8k**: HRMS(ESI) (MH$^+$) m/z: 794.42311, calcd for $C_{43}H_{60}N_3O_{11}$ 794.42224; ^{1}H NMR (400 MHz, CDCl$_3$) δ: [8.88 (d, J = 2.0 Hz, 1 H), 8.24 (d, J = 1.8 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.78 (d, J = 8.3 Hz, 1 H), 7.65–7.69 (m, 1 H), 7.51–7.55 (m, 1 H), 3-quinolyl], 5.05 (dd, J = 2.6, 10.0 Hz,1 H, H-13), 4.96 and 4.91 (d, J = 15.4 Hz, 2 H, C**H**$_2$C≡C–Ar), 4.80 (s, 1 H, H-11), 4.29 (d, J = 7.3 Hz, 1 H, H-1′), 4.19 (d, J = 8.4 Hz, 1 H, H-5), 3.51–3.84 (m, 3 H, H-2, H-8, H-5′), 3.20 (dd, J = 7.3 Hz, 10.2 Hz, 1 H, H-2′), 3.00–3.06 (m, 1 H, H-4), 2.73 (s, 3 H, 6-OCH$_3$), 2.44–2.57 (m, 2 H, H-3′, H-10), 2.27 (s, 6 H, –N(CH$_3$)$_2$), 1.89–1.93 (m, 1 H, H-14eq), 1.66–1.74 (m, 2 H, H-7, H-4′eq), 1.57 (s, 3 H, 12-CH$_3$), 1.46 (s, 3 H, 6-CH$_3$), 1.22–1.34 (m, 13 H, 4-CH$_3$, 10-CH$_3$, 5′-CH$_3$, 2-CH$_3$, H-4′ax), 1.08 (d, J = 6.8 Hz, 3 H, 8-CH$_3$), 0.89 (t, J = 7.4 Hz, 3 H, 15-CH$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 204.0, 169.1, 165.9, 159.5, 154.4, 152.1, 146.9, 138.8, 130.1, 129.4, 127.7, 127.2, 117.0, 103.6, 76.4, 70.3, 69.3, 66.1, 62.0, 51.2, 49.7, 47.8, 40.3, 29.3, 22.5, 21.1, 19.8, 18.9, 15.8, 14.3, 13.2, 10.4.

7.18. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(6′-quinolyl)-2-propargyl]oxime 11,12-cyclic carbonate (**8l**)

Following the procedure for the synthesis **7i** and **8i**, **7l** and **8l** were obtained from the coupling of **6** (0.700 g, 0.988 mmol) and 6-bromoquinoline (0.330 mL, 2.43 mmol) in yields of 8.8% and 23.0%, respectively. **8l**: HRMS (ESI) (MH$^+$) m/z 794.42082, calcd for $C_{43}H_{60}N_3O_{11}$ 794.42224; ^{1}H NMR (400 MHz, CDCl$_3$) δ: [8.90 (dd, J = 1.6 Hz, 4.4 Hz, 1 H), 8.11 (d, J = 8.0 Hz, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 7.93 (s, 1 H), 7.69 (dd, J = 1.6 Hz, 8.8 Hz, 1 H), 7.41 (q, J = 4.4 Hz, 1 H), 6-quinolyl], 5.04 (dd, J = 2.4 Hz, 10.0 Hz, 1 H, H-13), 4.94 and 4.89 (d, J = 15.6 Hz, 2 H, C**H**$_2$–C≡C–Ar), 4.81 (s, 1 H, H-11), 4.29 (d, J = 7.6 Hz, 1 H, H-1′), 4.18 (d, J = 8.4 Hz, 1 H, H-5), 3.77 (br, 1 H, H-2), 3.49–3.56 (m, 2 H, H-5′, H-8), 3.21 (dd, J = 7.6 Hz, 10.0 Hz, 1 H, H-2′), 2.99–3.08 (m, 1 H, H-4), 2.73 (s, 3 H, 6-OCH$_3$), 2.46–2.58 (m, 2 H, H-3′, H-10), 2.29 (s, 6 H, -N(CH$_3$)$_2$), 1.89–1.95 (m, 1 H, H-14eq), 1.72 (d, 1 H), 1.68 (d, 1 H), 1.57 (s, 3 H, 12-CH$_3$), 1.46 (s, 3 H, 6-CH$_3$), 1.23–1.32 (m, 13 H, 2-CH$_3$, 4-CH$_3$, 10-CH$_3$, 5′-CH$_3$, H-4′ax), 1.02 (d, J = 6.4 Hz, 3 H, 8-CH$_3$), 0.89 (t, J = 7.2 Hz, 3 H, 15-CH$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 204.0, 169.0, 165.7, 154.4, 150.9, 147.7, 135.8, 132.2, 131.4, 129.5, 128.0, 121.7, 121.2, 103.8, 87.0, 85.5, 84.8, 82.8, 79.5, 78.5, 77.2, 76.4, 70.4, 69.5, 65.6, 62.1, 51.2, 49.7, 47.9, 40.4, 40.2, 38.4, 28.3, 26.5, 22.5, 21.2, 19.8, 18.9, 15.9, 15.5, 14.3, 13.3, 10.4.

7.19. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(3′-quinolyl)-2-propyl]oxime 11,12-cyclic carbonate (**10k**)

To a solution of **9k** [27] (0.254 g, 0.319 mmol) in MeOH (10 mL) were added HCOONH$_4$ (0.200 g, 3.19 mmol), HCOOH (0.24 mL, 6.38 mmol), and 10% Pd–C (0.13 g). The reaction mixture was flushed with hydrogen and sealed in a pressure tube, and then was stirred at 65 °C for 24 h. 10% Pd–C was removed by filtration before the solvent was evaporated. The residue was dissolved in CH_2Cl_2, and aqueous NaOH (2 mol/L) was added to adjust the pH to ≥9. Additional water (20 mL) was added, and the mixture was stirred for 20 min. The organic phase was washed with brine (20 mL) and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (5:5:0.2 petroleum ether/acetone/triethylamine) to yield **10k** (47 mg, 18.7%). **10k**: HRMS (ESI) (M + H)$^+$ m/z 798.45416, calcd for $C_{43}H_{64}N_3O_{11}$ 798.45354.^{1}H NMR (400 MHz, CDCl$_3$) δ: [8.78 (d, J = 2.0 Hz, 1 H), 8.07 (d, J = 8.4 Hz, 1 H), 7.98 (s, 1 H), 7.79 (d, J = 8.4 Hz, 1 H), 7.63–7.67 (m, 1 H), 7.50–7.53 (m, 1 H), 3-quinolyl], 5.05 (dd, J = 2.4, 10.0 Hz,1 H, H-13), 4.79 (s, 1 H, H-11), 4.30 (d, J = 7.2 Hz, 1 H, H-1′), 4.19 (d, J = 8.4 Hz, 1 H, H-5), 4.03–4.15 (m, 2 H, –C**H**$_2$–CH$_2$–CH$_2$–Ar), 3.82 (q, J = 6.8 Hz, 1 H, H-2), 3.53–3.56 (m, 2 H, H-8, H-5′), 3.20–3.25 (m, 1 H, H-2′), 3.01–3.09 (m, 1 H, H-4), 2.84–2.91 (m, 2 H, –CH$_2$–CH$_2$–C**H**$_2$–Ar), 2.70 (s, 3 H, 6-OCH$_3$), 2.45–2.56 (m, 2 H, H-3′, H-10), 2.30 (s, 6 H, -N(CH$_3$)$_2$), 1.99–2.17 (m, 2 H, –CH$_2$–C**H**$_2$–CH$_2$–Ar), 1.86–1.94 (m, 1 H, H-14eq), 1.62–1.72 (m, 2 H, H-7, H-4′eq), 1.56 (s, 3 H, 12-CH$_3$), 1.42 (s, 3 H, 6-CH$_3$), 1.37 (d, J = 6.8 Hz, 3 H, 2-CH$_3$), 1.20–1.28 (m,

10 H, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 0.99 (d, $J = 6.8$ Hz, 3 H, 8-CH_3), 0.90 (t, $J = 7.6$ Hz, 3 H, 15-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 203.9, 169.1, 164.1, 154.4, 152.0, 146.8, 134.6, 134.4, 129.0, 128.6, 128.2, 127.4, 126.6, 103.8, 84.8, 82.8, 79.4, 78.5, 76.4, 72.2, 70.3, 69.4, 65.9, 51.2, 49.7, 47.9, 40.3, 40.2, 38.4, 30.6, 29.6, 28.7, 26.3, 22.5, 21.2, 19.8, 19.0, 15.9, 15.4, 14.3, 13.2, 10.4.

*7.20. 3-O-Descladinosyl-3-keto-6-O-methylerythromycin A E-9-O-[3-(4′-isoquinolyl)-2-propyl]oxime 11,12-cyclic carbonate (**10i**)*

To a solution of **8i** (0.162 g, 0.204 mmol) in MeOH (10 mL) were added $HCOONH_4$ (0.130 g, 2.04 mmol), HCOOH (0.15 mL, 4.08 mmol), and 10% Pd–C (81 mg). The reaction mixture was flushed with hydrogen and sealed in a pressure tube, and then was stirred at 65 °C for 24 h. 10% Pd–C was removed by filtration before the solvent was evaporated. The residue was dissolved in CH_2Cl_2, and aqueous NaOH (2 mol/L) was added to adjust the pH to ≥9. Additional water (20 mL) was added, and the mixture was stirred for 20 min. The organic phase was washed with brine (20 mL) and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (5:5:0.2 petroleum ether/acetone/triethylamine) to yield **10i** (57 mg, 0.07 mmol, 34.8%). **10i**: HRMS (ESI) $(M + H)^+$ *m/z* 798.45260, calcd for $C_{43}H_{64}N_3O_{11}$ 798.45354.^{1}H NMR (400 MHz, $CDCl_3$) δ: [9.08 (s, 1 H), 8.34 (s, 1 H), 7.92–7.98 (m, 2 H), 7.57–7.70 (m, 2 H), 4-isoquinolyl], 5.00 (dd, $J = 2.8, 10.0$ Hz, 1 H, H-13), 4.75 (s, 1 H, H-11), 4.25 (d, $J = 7.2$ Hz, 1 H, H-1′), 4.05–4.16 (m, 3 H, H-5, −C**H**$_2$−CH_2−CH_2−Ar), 3.49–3.78 (m, 3 H, H-2, H-8, H-5′), 2.91–3.22 (m, 4 H, H-2′, H-4, −CH_2−CH_2−C**H**$_2$−Ar), 2.63 (s, 3 H, 6-OCH_3), 2.39–2.53 (m, 2 H, H-3′, H-10), 2.23 (s, 6 H, −$N(CH_3)_2$), 2.03–2.13 (m, 2 H, −CH_2−C**H**$_2$−CH_2−Ar), 1.61–1.86 (m, 3 H, H-14eq, H-7, H-4′eq), 1.51 (s, 3 H, 12-CH_3), 1.39 (s, 3 H, 6-CH_3), 1.15–1.33 (m, 13 H, 2-CH_3, 4-CH_3, 10-CH_3, 5′-CH_3, H-4′ax), 0.94 (m, 3 H, 8-CH_3), 0.85 (t, $J = 7.2$ Hz, 3 H, 15-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 203.9, 169.1, 164.2, 154.4, 151.2, 142.6, 134.7, 131.1, 130.2, 128.3, 127.3, 126.9, 123.0, 103.9, 84.8, 82.8, 79.4, 78.5, 76.4, 72.6, 70.4, 69.5, 65.8, 51.2, 49.7, 47.9, 46.0, 40.3, 38.4, 30.1, 28.5, 26.7, 22.5, 21.2, 19.8, 19.0, 15.9, 15.4, 14.3, 13.2, 10.4.

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