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Novel hybrids of 15-membered 8a- and 9a-azahomoerythromycin A ketolides and quinolones as potent antibacterials

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ABSTRACT

A series of novel 6-O-substituted and 6,12-di-O-substituted 8a-aza-8a-homoerythromycin A and 9a-aza-9a-homoerythromycin A ketolides were synthesized and evaluated for in vitro antibacterial activity against a panel of representative erythromycin-susceptible and erythromycin-resistant test strains. Another series of ketolides based on 14-membered erythromycin oxime scaffold was also synthesized and their antibacterial activity compared to those of 15-membered azahomoerythromycin analogues. In general, structure–activity studies have shown that 14-membered ketolides displayed favorable antibacterial activity in comparison to their corresponding 15-membered analogues within 9a-azahomoerythromycin series. However, within 8a-azahomoerythromycin series, some compounds incorporating a ketolide combined with either quinoline or quinolone pharmacophore substructures showed significantly potent activity against a variety of erythromycin-susceptible and macrolide-lincosamide-streptogramin B (MLS_B)-resistant Gram-positive pathogens as well as fastidious Gram-negative pathogens. The best compounds in this series overcome all types of resistance in relevant clinical Gram-positive pathogens and display hitherto unprecedented in vitro activity against the constitutively MLS_B-resistant strain of *Staphylococcus aureus*. In addition, they also represent an improvement over telithromycin (**2**) and cethromycin (**3**) against fastidious Gram-negative pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*.

1. Introduction

The most advanced new series of semisynthetic derivatives of erythromycin A (**1**) (Fig. 1) are the ketolides, named according to their common feature, a ketone at the C-3 position of the macrolactone ring instead of L-cladinose sugar found in erythromycin.[1] Their most interesting and potentially useful microbiological attributes are their lack of induction of MLS_B resistance, and their activity against certain respiratory tract bacteria that are resistant to other macrolides. Most prominent members of this generation of macrolides characterize an 11,12-cyclic carbamate group within the aglycon ring, and an aryl-alkenyl or heteroaryl-alkenyl group in the side chain. The ketolide telithromycin **2** (formerly known as HMR 3647)[2] is not only less prone to induce resistance than other macrolide antibiotics, but also displays good pharmacokinetic parameters in vivo, as well as high therapeutic efficacy in mice that were infected with respiratory pathogens. Recently, it has been proven that the C-11,C-12 cyclic carbamate present in telithromycin and cethromycin (**3**, ABT-773)[3] can be replaced by properly functionalized C-11,C-12 α-amino lactone ring. This type of modification led to a novel GlaxoSmithKline lead series exemplified by the prototype ketolide antibiotic GW773546X (**4**) (Fig. 1).[4] Recent studies in this area have unveiled a novel series of orally active C-6 substituted carbamate ketolides based on 14-membered erythromycin A (Ery A) scaffold.[5] The most promising analogues within this series, **5** and **6**, were found to provide good oral activity in mice that was essentially equivalent to **2** (Fig. 1).

The synthesis of ketolides based on a 15-membered ring azahomoerythromycin A skeleton represents a logical extension of the success of 14-membered ring ketolides.[6] However, in contrast to 14-membered ketolides the structure–activity relationships of their corresponding 15-membered analogues have been relatively unexplored, and no systematic study on the structure–activity relationship for 6-O-substitued and 6,12-di-O-substituted 15-membered azaketolides has been reported so far.[7] Recently, a number of 6-O-substituted 15-membered azahomoerythromycin derivatives have been reported, but none of them exhibited antibacterial activity against constitutively MLS_B-resistant strains.[8]

Abbreviations: Ery A, erythromycin A; MLS_B, macrolide-lincosamide-streptogramin B; EDC HCl, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; PyTFA, pyridinium trifluoroacetate.

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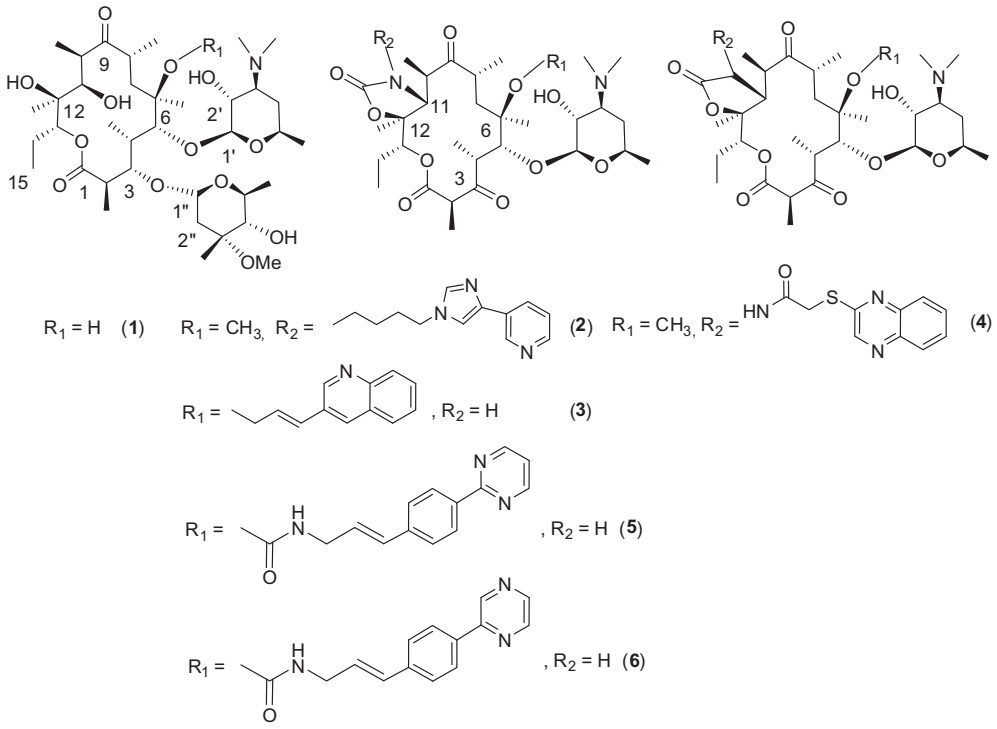


Figure 1. Structures of novel ketolides based on erythromycin A (**1**): telithromycin (**2**), cethromycin (**3**), GW773546X (**4**), JNJ-17069546 (**5**), and JNJ-17070885 (**6**).

A therapeutically useful objective of our discovery research program was to find novel macrolide derivatives with improved activity against clinically relevant macrolide-resistant respiratory pathogens, and would additionally provide in vivo efficacy against important both gram-positive and gram-negative pathogens, especially those such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* that are causative agents of respiratory infections in humans. In addition to broadening the spectrum of susceptible and resistant organisms, other initial research goals included improvement of pharmacokinetic parameters such as greater oral bioavailability and a longer in vivo half-life to reduce the frequency of dosing and quantities of compounds administered. A new agent incorporating features such as these would constitute a significant new discovery that would substantially expand the therapeutic utility of macrolide antibiotics.

In this paper, we describe the synthesis of a series of novel 6-O-substituted 8a- and 9a-azahomoerythromycin A ketolides and their antibacterial activity against some key erythromycin-resistant pathogens. The new ketolides have two important structural features in common: first of all, an aryl or heteroaryl group attached at the C-6 position of the macrolide scaffold for improving activity against MLS_B resistance, and secondly, a ketolide backbone for improving potency and activity against efflux resistance. Thus, in the 8a- and 9a-azahomoerythromycin series, a variety of aryl and heteroaryl substituents were introduced at the C-6 position (Chart 1) that was coupled with a carbonyl group at the C-3 position.

In addition, following the structure–activity relationships obtained in our laboratories over the years, a cyclic carbonate constraint was introduced at the C-11,12 position of azahomoerythromycin scaffold for improving potency and activity against macrolide-resistant organisms. In this paper we also report the synthesis and antibacterial evaluation of a novel series of 6,12-di-O-substituted 9a-aza-9a-homoerythromycin ketolides. For the comparison with the 15-membered series, a representative set of 14-membered ketolides based on erythromycin A oxime scaffold was also prepared and evaluated for antibacterial activity.

2. Results and discussion

2.1. Chemistry

We have recently developed an efficient and versatile synthetic methodology to access a wide range of 15-membered 8a-azahomoerythromycin A analogues.[9] This report will highlight the synthesis and in vitro antibacterial activity of a series of novel 6-O-substituted and 6,12-di-O-substituted 8a- and 9a-azahomoerythromycin A analogues. 6-*O*-allyl-8a-aza-8a-homoerythromycin A (**9**) and its corresponding 9a-aza-9a-homoerythromycin A analogue (**10**) were prepared, as illustrated in Scheme 1, by *E*–*Z* isomerization-Beckmann rearrangement methodology. On the other hand, Beckmann rearrangement of 6,12-di-*O*-allylEry A 9(*E*)-oxime (**12**)[9] resulted in the formation of 3-*O*-descladinosyl-6,12-di-*O*-allyl-9a-aza-9a-homoerythromycin (**13**).

In this work we have used 6-*O*-allylerythromycin A 9(*E*)-oxime (**11**) as a convenient source of starting material for further chemical modification leading to the ketolide series. The oxime **11** was readily synthesized in four steps starting from commercially available Ery A 9(*E*)-oxime.[10] The cladinose sugar was selectively hydrolyzed by treating **11** with 2 M HCl in ethanol for 12 h at room temperature to give descladinosyl intermediate **7** (Scheme 1). The cladinose-related by-products were removed in the aqueous workup, whereas epimeric 3-*O*-descladinosyl 6-*O*-allylerythromycin 9(*E*)-oxime **7** was advanced into the next step without further purification. Base-induced isomerization of **7** proceeded stereoselectively to give the corresponding epimeric oxime (**8**) of predominantly *Z* stereochemistry (9:1 epimeric mixture of *Z*/*E* oximes) in 70% yield over two steps. Both oximes (**7** and **8**) were used as precursors in a subsequent Beckmann rearrangement reaction as depicted in Scheme 1. Beckmann rearrangement of the *Z* isomer of 3-*O*-descladinosyl-6-*O*-allylerythromycin oxime (**8**) with *p*-tosyl chloride and sodium bicarbonate in aqueous acetone afforded 15-membered 8a-lactam **9** in 90% isolated yield. On the other hand ring enlargement of descladinosyl-6-*O*-allylerythromycin-9(*E*)-oxime (**7**) yielded 9a-lactam **10** in 85% yield. During these studies

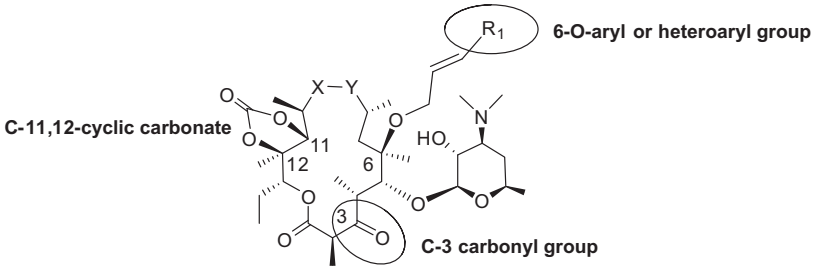
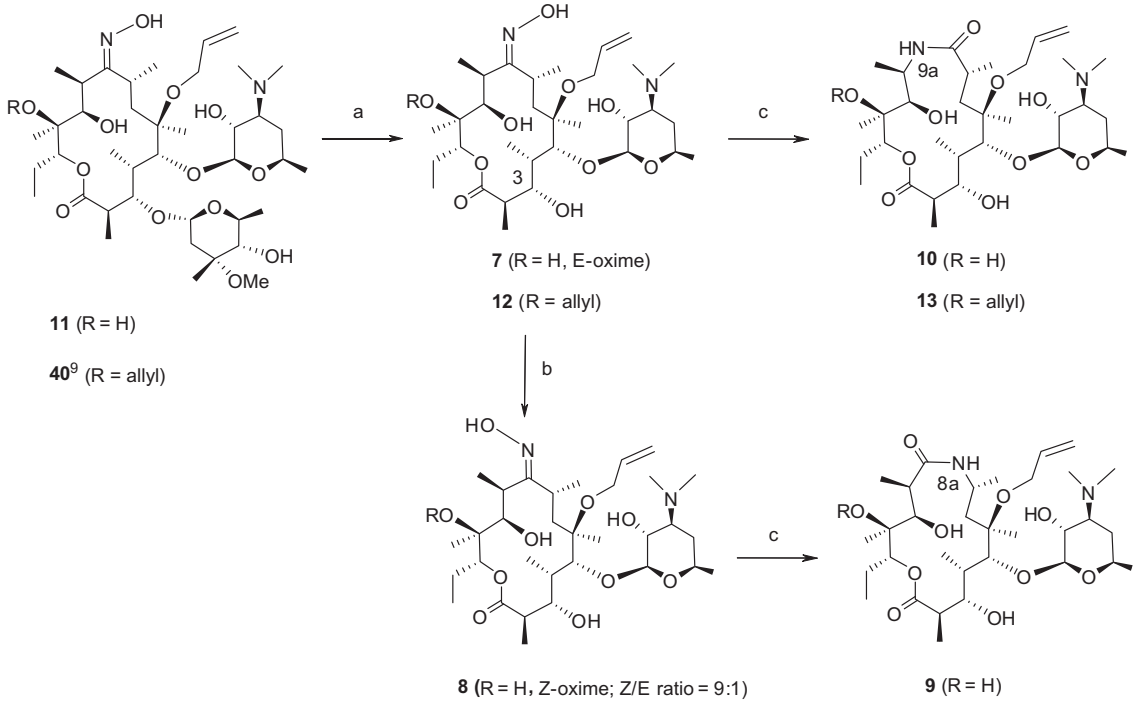


Chart 1. Structural features included in the design of novel 15-membered macrolides.



Scheme 1. Base-induced isomerization and Beckmann rearrangement of 3-*O*-descladinosyl-6-*O*-allylEry A 9(*E*)- and 9(*Z*)-oximes (**7** and **8**), and 3-*O*-descladinosyl-6,12-di-*O*-allylEry A 9(*E*)-oxime (**12**). Reagents and conditions: (a) HCl, EtOH/H_2O (2:1), 90%; (b) LiOH × H_2O, EtOH, 80%; (c) *p*-TsCl, $NaHCO_3$, acetone/H_2O (1:1), 75–90%.

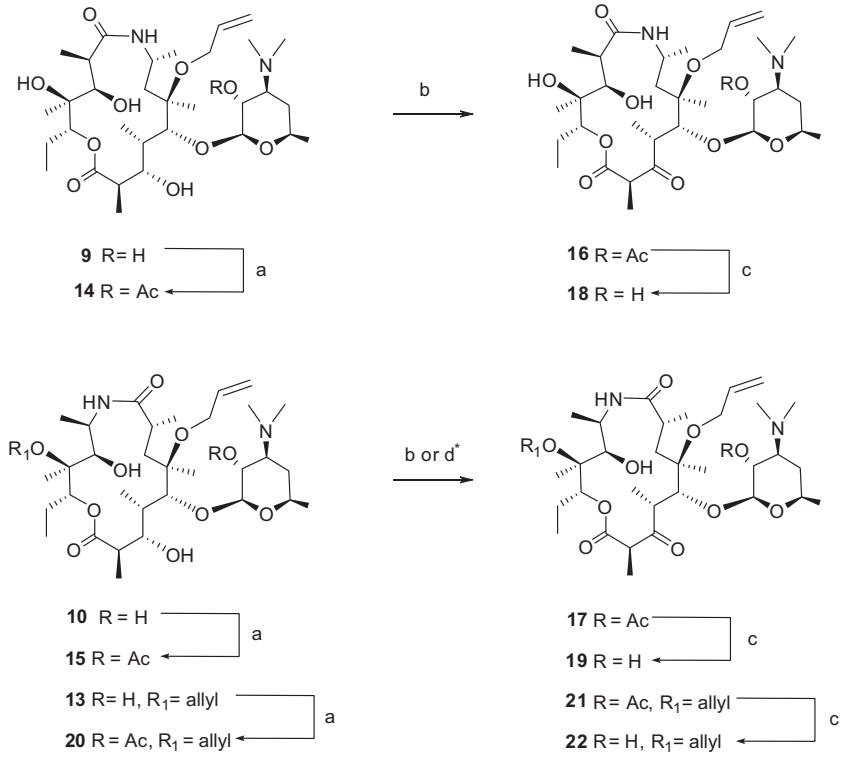
we also proved that the Beckmann rearrangement could be readily applied to other 14-membered ring macrolides. For example, ring enlargement of descladinosyl-6,12-di-*O*-allylerythromycin-9(*E*)-oxime (**12**)[9] under the same reaction conditions as those applied in Beckmann rearrangement of **7** and **8**, provided the corresponding 9a-azahomoerythromycin A analogue **13** in 75% yield, as outlined in Scheme 1.[‡]

As indicated in Scheme 2, selective protection of the C-2′-hydroxyl group in descladinosyl lactams **9** and **10** was accomplished by acylation with acetic anhydride and trietylamine at room temperature. Acetyl derivatives **14** and **15** thus obtained were oxidized with excess Dess–Martin periodinane[11] in the presence of pyridine and $NaHCO_3$ to furnish the corresponding ketolides **16** and **17**. These compounds were deprotected by treatment in refluxing methanol to provide the ketolides **18** and **19** in high yield. On the other hand, oxidation of 3-*O*-descladinosyl-6,12-di-*O*-allyl-9a-aza-9a-homoerythromycin (**13**) was accomplished by using modified Pfitzner–Moffat[12] conditions: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC HCl)/DMSO/pyridinium trifluoroacetate in methylene chloride at room temperature (Scheme 2). Acylation of **13** with acetic anhydride and triethylamine led smoothly to C-2′ acetate **20**. Pfitzner–Moffat oxidation of the C-3 hydroxyl group followed by methanolysis of C-2′ acetate (**21**) provided the desired ketolide **22** in 78% overall yield.

These compounds served as the key intermediates for the preparation of wide range of analogs bearing an aryl or heteroaryl moiety (Scheme 3). Introduction of an aryl or heteroaryl moieties to the allyl side chain of **18**, **19**, and **22** was achieved by utilizing Heck coupling reaction.[13] Under optimized conditions ($Pd(OAc)_2$/P(*o*-tolyl)$_3$/Et_3N/CH_3CN), a basic series of 6-O-substituted ketolides with naphthyl (**a**) and quinolyl groups (**b** and **c**) tethered to the C-6 position was prepared (Chart 2).

From 6-*O*-allyl-8a-aza-8a-homoerythromycin A ketolide (**18**), another series of ketolide analogues was prepared by nucleophilic ring opening of *syn*- and *anti*-epoxy 8a-lactams (**27a** and **27b**) with amines **a–m** (Chart 3) following our published protocol (Scheme 4).[9] Nucleophilic ring opening afforded a mixture of diastereoisomeric

[‡] Precursor for the Beckmann rearrangement **12** was readily obtained from 6,12-di-*O*-allylerythromycin-9(*E*)-oxime (**40**) according to our published procedure.[9]



Scheme 2. Dess–Martin oxidation of 3-descladinosyl-6-*O*-allyl-8a-aza-8a-homoEry A (**9**) and 3-descladinosyl-6-*O*-allyl-9a-aza-9a-homoEry A (**10**), and Pfitzner–Moffat oxidation of 3-descladinosyl-6,12-di-*O*-allyl-9a-aza-9a-homoEry A (**13**). Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, 90%; (b) Dess–Martin-periodinane, pyridine, $NaHCO_3$, CH_2Cl_2, 90%; (c) MeOH, reflux, 90%; (d) EDC HCl, DMSO, PyTFA, CH_2Cl_2, 78% (* used for the synthesis of **22**).

β-amino alcohols (**28aa–am** and **28ba–bm**) that were not easily separable by flash chromatography.

As described in the literature[16] lithium perchlorate was added to facilitate the ring opening of the epoxide owing to the coordination of the lithium ion with the oxygen atom. Typically a fivefold excess of amine as well as lithium perchlorate was used in this procedure and the reactions were carried out in refluxing 2-propanol.

In continuation of our studies, we have synthesized 3-*O*-descladinosyl-3-oxo-6-*O*-(3-quinolyl-2-propenyl)erythromycin A 9(*E*)-oxime (**33**) starting from readily accessible key intermediate, 9,2′-di-*O*-acetyl-3-*O*-descladinosyl-3-oxo-6-*O*-allylerythromycin A 9(*E*)-oxime (**30**). The synthesis of key intermediate **30** (Scheme 5) started with a known 3-descladinosyl Ery 9(*E*)-oxime (**7**) which was acetylated by exposure to excess acetic anhydride and triethylamine at room temperature to afford the protected oxime **29** in 90% yield.

Dess–Martin oxidation of **29** in methylene chloride at room temperature provided the corresponding ketolide **30**, which was subjected to Heck coupling with 3-bromoquinoline in the presence of a catalytic amount of palladium(II) acetate and tri-*O*-tolyl phosphine to give 6-*O*-allylquinolyl oxime **31**. Subsequent methanolysis of the C-2′ acetate at room temperature gave **32**, which was fully deprotected by exposure to triethylamine in refluxing methanol to afford the target compound **33** in 78% yield over two steps.

As it has been shown earlier that introduction of fused heterocycles such as carbonates[17] and carbamates[18] at the C-11, C-12 positions of the macrolides lead to improvement of the antimicrobial activity we envisioned the introduction of the C-11, C-12 cyclic carbonate onto the main framework of 8a-azaketolide **23b**. The synthesis of cyclic carbonate **34** was achieved by treatment of **23b** with ethylene carbonate in the presence of K_2CO_3 in refluxing toluene, as illustrated in Scheme 6.

6-*O*-Hexahydroquinolylpropyl ketolide **35**, a derivative with a saturated linker between the heteroaryl group and the lactone ring, was prepared by catalytic hydrogenation of **23b** (Scheme 6). For comparison of antimicrobial activity, 6-*O*-(3-aryl-2-propenyl)-8a-aza-8a-homoerythromycin A derivatives **37a–c** (Ar = Ph, 3-quinolyl, 4-quinolyl) and 6-*O*-[3-(3′-quinolyl)-2-propenyl]-9a-aza-9a-homoerythromycin A (**39b**) were prepared by Heck coupling of 6-*O*-allyl-8a-lactam **36** and 6-*O*-allyl-9a-lactam **38**, respectively, as depicted in Scheme 7.

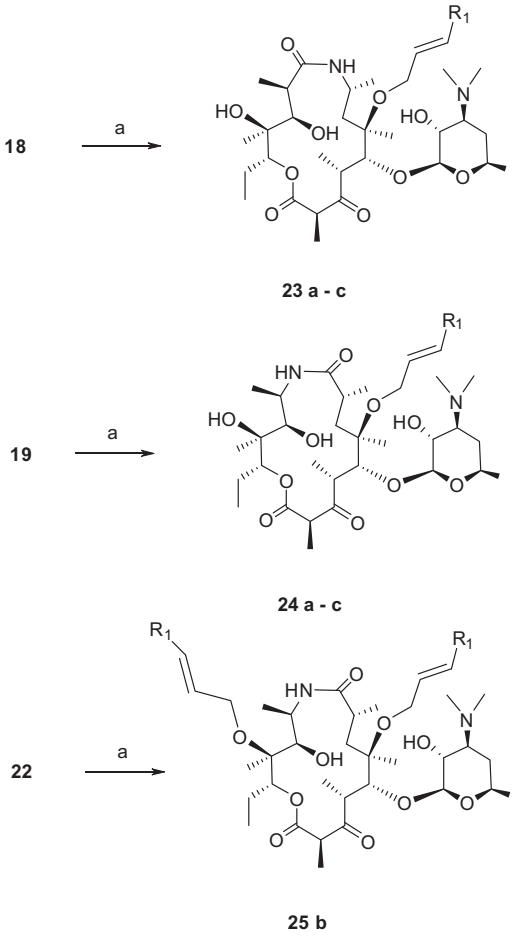
2.2. Antibacterial activity

The antibacterial activity of the 6-O-substituted and 6,12-di-O-substituted azaketolides was tested against a panel of representative pathogens selected from the PLIVA Research Institute clinical culture collection. The in vitro antibacterial activity is reported as the minimum inhibitory concentrations (MICs), which were determined by the agar microdilution method according to NCCLS standards.[19] Table 1 shows in vitro activity of a selected group of azaketolide analogues and the reference compounds, ciprofloxacin (**40**), telithromycin (**2**), cethromycin (**3**) and azithromycin.

2.2.1. Structure–activity relationships of aryl- and heteroaryl-substituted 8a- and 9a-azaketolides

Aryl and heteroaryl moieties substituted at the C-6 position of the macrolide core are presumed to play a crucial role in binding to domain II of the 23S rRNA.[20] Consequently, extensive modifications of this side chain have been carried out on the most active 8a-azaketolide core (**18**).

The structure–activity relationship analysis of the macrolide subgroup of 8a-aza-8a-homoerythromycin A ketolides have unveiled a combination of key structural features that contribute significantly to enhancement of the antibacterial activity. These features comprise a conformationally constrained propenyl linker and a heteroaryl moiety attached to the C-6 position of the 8a-azaketolide core. In general, the compounds containing a bicyclic



Scheme 3. Modification of 6-*O*-allyl ketolides **18**, **19**, and **22** via Heck reaction. Reagents and conditions: (a) ArX (X = Br or I), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 100 °C, 50–80%.

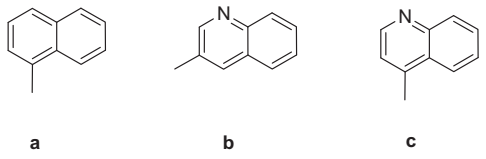


Chart 2. Structures of aryl and heteroaryl groups (R_1).

heteroaryl moiety in the side chain were more active against highly macrolide-resistant strains of *S. pneumoniae* and *Streptococcus pyogenes* (B0627 and B0544) than compounds containing monocyclic aryl moieties. The 15-membered 8a-lactams generally maintained good activity against the erythromycin-susceptible pathogens as well as inducibly- and efflux-resistant strains of *Staphylococcus aureus*, *S. pyogenes* and *S. pneumoniae*. While most of the ketolides of the 8a-lactam series were still inactive against the constitutively-resistant pathogens, some of them, especially ketolides with a 'cethromycin-like' side chain, started to show moderate activity against these organisms. The most potent compounds **23b**, **28ab–bb**, and **34** out of this series showed similar antimicrobial spectrum, and with the exception of the constitutively-resistant strains of *S. pneumoniae* and *S. pyogenes* almost comparable in vitro activity as the reference ketolide cethromycin (**3**). In addition, a few compounds within the 8a-azaketolide series (i.e., **28ab–bb**, **28ac–bc**, and **28ae–be**) showed increased activity against *H. influenzae* as compared to **3**.

The introduction of a more polar amide group instead of a C-9 carbonyl group of erythromycin A resulted in a very different profile of activity. All the compounds tested within the 8a-lactam and 9a-lactam non-ketolide series showed antibacterial activity similar to azithromycin. While they were all effective against the erythromycin-sensitive strains, they were essentially inactive against the MLS_B-resistant strains regardless of the phenotype carried. In all cases studied the non-ketolide 8a-lactams gave significantly better activity than the corresponding 9a-lactam counterparts (e.g., **36** vs **38**, **37b** vs **39b**). Some of the 8a-lactam compounds (**36**, **37b, 37c**) exhibited excellent activity against the erythromycin-sensitive strains, while they were all essentially inactive against most of the MLS_B-resistant strains. Removal of the L-cladinosyl moiety of 8a-aza-8a-homoerythromycin A (**36**) resulted in a complete loss of antibacterial activity (MICs > 64 μg/mL). Simple introduction of a keto group at the C-3 position did not completely restore the antibacterial activity, although it seemed that the ketolide **18** was significantly more effective than its respective macrolide analogue **36** against the inducibly MLS_B-resistant and efflux-resistant strains of *S. aureus*. Furthermore, ketolide **18** was equally active against the erythromycin-sensitive and inducibly-resistant strains of *S. aureus*, each having a MIC of 2 μg/mL. The same trend was observed when macrolide **37b** and the corresponding ketolide **23b** were compared against the efflux-resistant strain of *S. aureus*. For instance, macrolide **37b** was 128-fold less active against efflux strain *S. aureus* B0331 as compared to its activity against the sensitive *S. aureus* B0329 strain. However, the corresponding ketolide **23b** was significantly more active against efflux resistance, having a MIC of 0.5 μg/mL. The difference between activities against sensitive and efflux strains was only twofold. This insensitivity to efflux and inducibility is in accordance with the literature precedence for other ketolides.[21]

As shown in Table 1, the antibacterial activity of the 8a-azaketolide series was clearly superior to that of the corresponding 9a-azaketolide analogues regardless of the side chain attached to the C-6 position (**23b** vs **24b** and **18** vs **19**). The synthesis of the 8a-azaketolides **28ab–bb** and **34** made us very confident in the antimicrobial potential of the ketolide family. Analogues with an aryl or heteroaryl group tethered to the C-6 position of the ketolide skeleton generally showed improved activity against MLS_B-resistant strains. In addition, these analogues also exhibited improved activity against inducibly MLS_B-resistant *S. aureus* and efflux resistance. The significant effect of the C-6 heteroaryl group on antibacterial activity could be demonstrated by comparing 6-*O*-allyl ketolides **18** and **22**, with their corresponding quinolyl analogues **23b** and **25b**, respectively. In particular, compounds **23b** and **25b** exhibited significantly improved activity against constitutively MLS_B-resistant *S. pneumoniae* (MIC = 16 and 4 μg/mL, respectively) as well as inducibly MLS_B-resistant strains of *S. aureus* and *S. pyogenes* with MICs between 0.25 and 1 μg/mL compared to **18** and **22**. On the other hand, 14-membered ketolides **32** and **33** showed almost the same activity against constitutively-resistant *S. pneumoniae* (MICs = 8 and 4 μg/mL, respectively), and were 4–8-fold more active then 15-membered quinolyl analogues **23b** and **25b** against inducibly-resistant *S. pyogenes*. The effectiveness of the C-6 heteroaryl structure on constitutively MLS_B-resistant strains can best be illustrated by comparing ketolides **18** and **23b**. The 6-*O*-allyl ketolide **18** and its quinolyl-substituted analogue **23b** showed almost similar activities against various sensitive strains. In contrast, compound **23b** displayed significantly improved activity against the constitutively MLS_B-resistant strains of *S. pneumoniae* and *S. pyogenes*. However, the 6-*O*-allylquinolyl ketolides (**23b** and **25b**) were still inactive against the constitutively MLS_B-resistant *S. aureus* strain B0330, having MICs > 64 μg/mL. The antibacterial activity of the 6-*O*-allylquinolyl substituted ketolide **23b** was further enhanced when an 11,12-cyclic carbonate group was

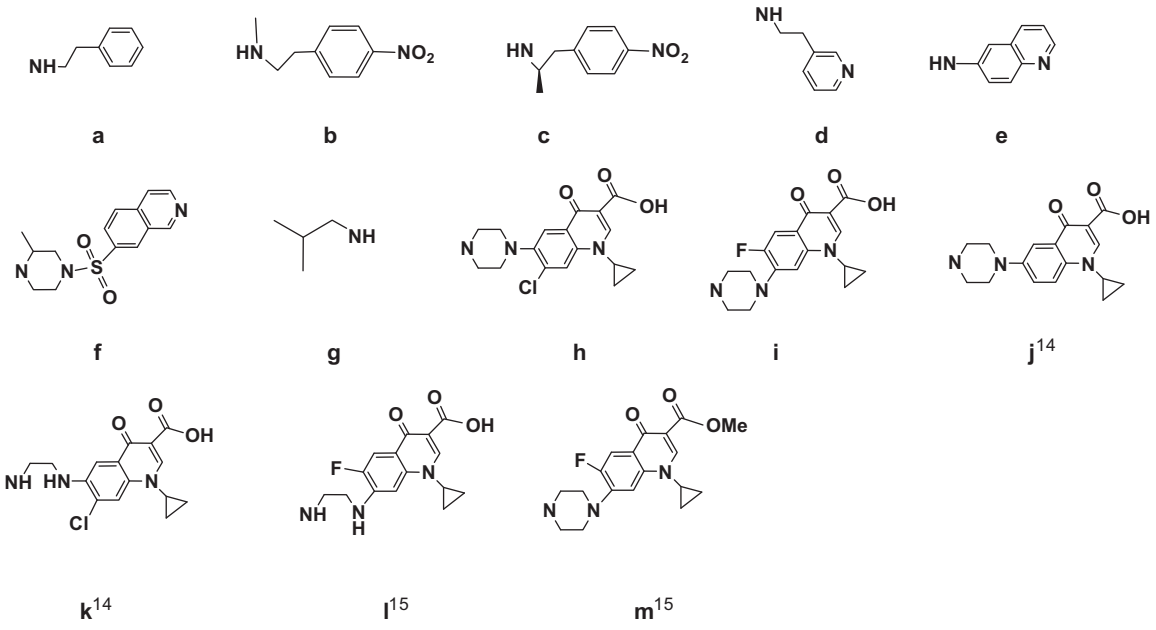
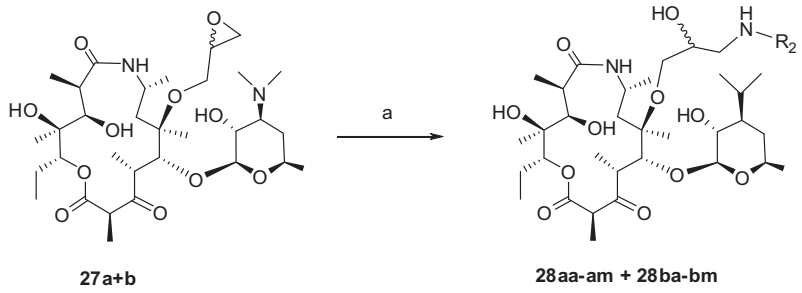


Chart 3. Amines employed as the R_2 substituent in ketolide series. See above mentioned reference for further information.



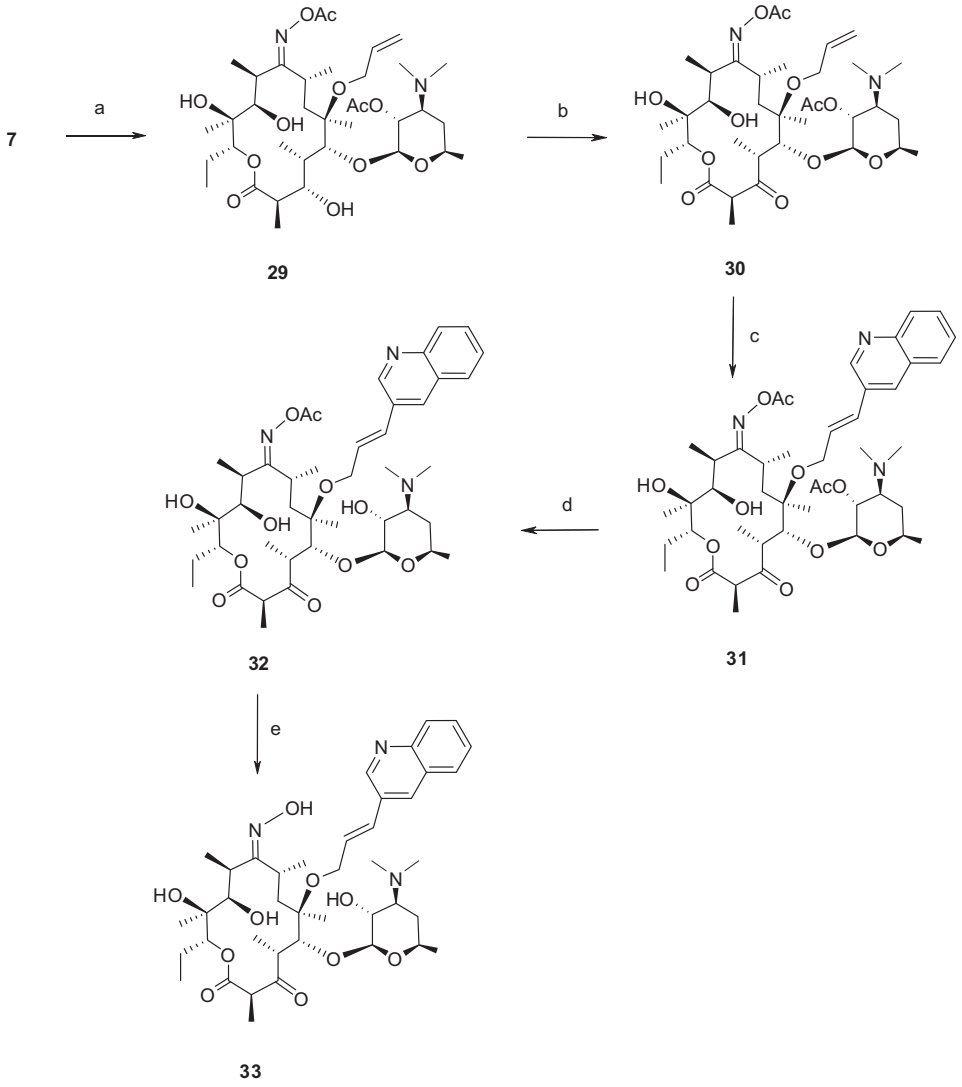
Scheme 4. Synthesis of 6-O-substituted 8a-aza-8a-homoEry A ketolides (**28aa–am** and **28ba–bm**). Reagents and conditions: (a) amine **a–m**, $LiClO_4$ $3H_2O$, 2-propanol, reflux, 50–80%.

introduced. Biological evaluation of **34** demonstrates a surprisingly good spectrum of activity against inducibly MLS_B-resistant *S. aureus*, *S. pyogenes* and *H. influenzae*, and with an exception of the still moderate activity against constitutively MLS_B-resistant *S. pneumoniae* (MIC = 4 μg/mL) its overall activity is similar to that of telithromycin (**2**). The introduction of a second quinolyl group at the C-12 position of 9a-lactam ketolide **24b** significantly improved the antibacterial activity of the parent compound. In analogy with the cyclic carbonate derivative **34**, this improvement was reflected both, on the activity against constitutively MLS_B-resistant *S. pneumoniae* and *S. pyogenes*, as well as on the activity against inducibly MLS_B-resistant Gram-positive bacteria. Actually, the ketolide **25b** was ca. 8–16-fold more potent against constitutively MLS_B-resistant strains of *S. pneumoniae* and *S. pyogenes* than its monosubstituted derivative **24b**. 8a-Azaketolide **23b**, the 6-*O*-(3-quinolyl-2-propenyl) derivative, exhibited a 2–4-fold improvement in activity against most of the strains tested as compared to the corresponding 1-naphtyl and 6-quinolyl isomers (**23a** and **23c**). The linker structure connecting the ketolide core and the heteroaryl group appeared to be important as well. For example, the saturated propyl analogue **35** was less effective than the parent propenyl compound **23b**, particularly against efflux-resistant strains, and both inducibly and constitutively MLS_B-resistant strains of *S. aureus*, *S. pneumoniae*, and *S. pyogenes*. Among the 14-membered ketolides, the 6-*O*-allylquinolyl substituted compounds **32** and **33** provided the best activity against constitutively MLS_B-resistant *S. pneumoniae* and *S. pyogenes* as well as inducibly-resistant *S. aureus*, and *S. pyogenes*. Furthermore, the antibacterial activity of 6-*O*-allylquinolyl substituted derivatives of erythromycin A oxime (**32** and **33**) was comparable to that of azithromycin itself against susceptible strains, but significantly enhanced against the inducibly and constitutively MLS_B-resistant strains of *S. pneumoniae* and *S. pyogenes*. Compound **33** displayed the best activity among the 14-membered ketolides as well as 15-membered ketolides within 9a-azahomoerythromycin series, and exhibited 'cethromycin-like' antimicrobial spectrum. However, relatively weak activity against the *H. influenzae* strain B0529, in addition to mediocre activity against constitutively MLS_B-resistant *S. pneumoniae* as compared to telithromycin (**2**) and cethromycin (**3**) prevented this compound from being considered for further development.

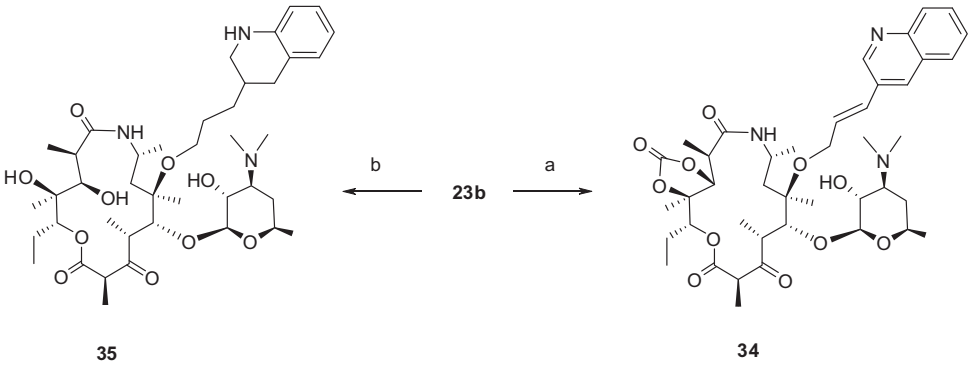
2.2.2. Structure–activity relationships of quinolone-substituted 8a-azaketolides

In an effort to overcome an intrinsic macrolide resistance against the constitutively MLS_B-resistant *S. aureus*, the effect of the 'ciprofloxacin-like' side chain component on the antibacterial activity of 8a-azaketolides was also examined in Table 2.

Therefore, we have prepared a series of ketolides in which a quinolone ring was appended to the macrolide core. To this end,

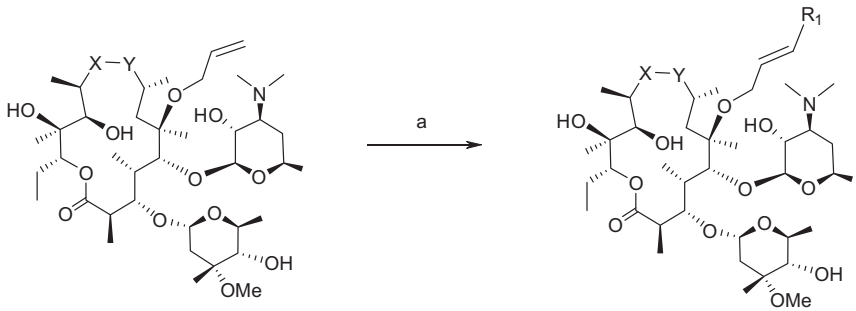


Scheme 5. Synthesis of 3-*O*-descladinosyl-3-oxo-6-*O*-(3-quinolyl-2-propenyl) Ery A 9(*E*)-oxime (**33**). Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, 85%; (b) Dess–Martin periodinane, Py, $NaHCO_3$, CH_2Cl_2, 78%; (c) 3-bromoquinoline, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 100 °C, 82%; (d) MeOH, rt, 70%; (e) Et_3N, MeOH, reflux, 75%.



Scheme 6. Synthesis of 6-*O*-[3-(3′-quinolyl)-2-propenyl]-8a-aza-8a-homoEry A 11,12-cyclocarbonate ketolide (**34**) and hexahydroquinolylpropyl ketolide (**35**). Reagents and conditions: (a) ethylene carbonate, K_2CO_3, toluene, reflux, 75%; (b) H_2, 10% Pd–C, MeOH, 62%.

a series of quinolone analogues **28ah–bh** to **28am–bm** was prepared and evaluated for in vitro antibacterial activity. It was found that the activity depends markedly on the point of attachment of the quinolone ring. The activity of the C-7 substituted quinolones **28ai** and **28bi** were in general 2–32-fold better than that of the C-6 substituted analogue **28ah–bh** against most strains. Furthermore, the design of a tether connecting the ketolide and quinolone pharmacophores appeared critical for antibacterial activity. Ethyleneamino-linked quinolone analogues **28ak–bk** and **28al–bl** were not as active as ketolides **28ah–bh**, **28ai**, **28bi**, and



36 X = CO, Y = NH

38 X = NH, Y = CO

37a-c X = CO, Y = NH

39b X = NH, Y = CO

Scheme 7. Synthesis of 6-O-substituted 8a-aza-8a-homoerythromycin A derivatives (**37a–c**) and 6-*O*-[3-(3′-quinolyl)-2-propenyl]-9a-aza-9a-homoerythromycin A (**39b**). Reagents and conditions: (a) R_1X (X = Br or I), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 100 °C, 55–82%.

Table 1
In vitro antibacterial activity of selected 6-O-substituted 8a-aza-8a-homoEry A and 9a-aza-9a-homoEry A ketolides, and 6,12-O-disubstituted 9a-aza-9a-homoEry A ketolides[a,b]

Compound	*S. aureus*				*S. pneumoniae*			*S. pyogenes*				*M. catarrhalis*	*H. influenzae*
	B0329 Ery-S	B0538 iMLS	B0330 cMLS	B0331 M	B0541 Ery-S	B0627 cMLS	B0326 M	B0542 Ery-S	B0543 iMLS	B0544 cMLS	B0545 M	B0324	B0529
18	2	2	>64	8	⩽0.125	>64	16	0.25	16	>64	8	⩽0.125	16
19	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	16	>64
22	8	8	>64	16	2	>64	4	2	32	>64	8	⩽0.125	16
23a	1	2	>64	4	⩽0.125	>64	2	0.25	4	>64	2	0.25	8
23b	1	0.5	>64	0.5	⩽0.125	16	0.5	⩽0.125	1	8	1	0.25	4
23c	0.5	1	>64	2	⩽0.125	>64	1	0.25	2	16	2	0.5	4
24b	8	16	>64	16	2	64	8	0.5	64	>64	4	2	32
25b	⩽0.125	0.25	>64	0.5	⩽0.125	4	0.5	⩽0.125	0.5	8	0.5	0.125	4
28aa–ba	4	16	>64	8	0.25	8	16	0.5	1	16	1	0.5	16
28ab–bb	⩽0.125	0.5	>64	1	⩽0.125	⩽0.125	0.5	⩽0.125	0.25	1	0.25	⩽0.125	1
28ac–bc	0.5	2	>64	2	⩽0.125	2	1	⩽0.125	0.5	4	0.5	0.25	1
28ad–bd	4	8	>64	4	0.5	2	8	0.25	4	32	2	1	8
28ae–be	2	2	64	1	⩽0.125	8	2	⩽0.125	4	16	8	0.5	⩽0.125
28af–bf	8	16	>64	16	⩽0.125	32	64	⩽0.125	16	>64	16	8	>64
28ag–bg	64	64	>64	64	16	>64	64	8	64	>64	8	16	>64
32	0.25	0.5	64	1	⩽0.125	8	⩽0.125	0.125	⩽0.125	32	0.5	8	32
33	⩽0.125	⩽0.125	>64	0.5	⩽0.125	4	⩽0.125	⩽0.125	⩽0.125	32	⩽0.125	4	8
34	⩽0.125	0.25	64	0.25	⩽0.06	4	⩽0.125	⩽0.125	⩽0.125	8	0.5	0.25	1
35	2	>64	64	64	⩽0.125	64	8	⩽0.125	16	>64	8	1	16
36	0.25	>64	>64	64	⩽0.125	>64	8	⩽0.125	16	>64	16	⩽0.125	1
37b	0.5	64	>64	32	⩽0.06	32	4	⩽0.06	2	>64	16	0.25	4
37c	0.5	>64	>64	64	⩽0.125	>64	64	⩽0.125	8	>64	32	2	16
38	>64	>64	>64	>64	>64	>64	>64	⩽0.125	4	>64	>64	4	64
39b	32	>64	>64	32	>64	>64	16	0.125	4	>64	16	8	64
40	0.125	16	⩽0.125	⩽0.125	⩽0.125	0.25	0.25	2	0.25	0.5	⩽0.125	0.125	⩽0.125
Azi	1	>64	>64	>64	⩽0.125	>64	4	⩽0.125	8	>64	1	0.25	1
2	⩽0.125	0.5	>64	0.25	⩽0.06	⩽0.125	0.5	⩽0.06	⩽0.06	4	0.25	⩽0.125	2
3	⩽0.06	0.25	>64	0.25	⩽0.06	⩽0.125	⩽0.06	⩽0.06	⩽0.06	1	⩽0.125	⩽0.125	2

Ery-S, erythromycin-susceptible strains; iMLS, inducibly-resistant strains; cMLS, constitutively-resistant strains; M, efflux-resistant strains; Azi, azithromycin.
[a] Minimum inhibitory concentration (MIC) values are given in μg/mL.
[b] All the compounds among the β-amino alcohol series except **28ai** and **28bi** were tested as diastereoisomeric mixtures.

28aj–bj incorporating ciprofloxacin and quinolone substructures linked via a piperazine group. Notably, the activity against a variety of susceptible and resistant Gram-positive and fastidious Gram-negative pathogens was markedly superior to azithromycin. In fact, the in vitro profile of **28ai** (*syn*-**28i**) compares favorably with telithromycin (**2**) and cethromycin (**3**). For example, compound **28ai** is almost as active as **3** against both constitutively MLS_B-resistant *S. pyogenes* and efflux-resistant *S. pneumoniae*. In addition, the antibacterial activity of **28ai** against the constitutively MLS_B-resistant *S. aureus* and Gram-negative bacteria was significantly improved in comparison to **2** and **3**. The macrolide-quinolone hybrids **28ak–bk** and **28al–bl**, which possess an aliphatic ethylenediamino-type linker, displayed an antibacterial spectrum similar to classical azaketolides by overcoming erythromycin efflux- and inducible-resistance in *S. aureus* (strains B0331, and B0538), *S. pneumoniae* (strain B0326) and *S. pyogenes* (strains B0545, and B0543). Additionally, and in analogy with the most azaketolides studied, activity against *S. pneumoniae* B0627 and *S. pyogenes* B0544, constitutively MLS_B-resistant strains, was somewhat lower than toward an efflux (*S. pneumoniae* B0326 and *S. pyogenes* B0545) and inducibly MLS_B-resistant strains (*S. aureus* B0538 and *S. pyogenes* B0543). In contrast, compounds **28ah–bh**, **28ai–bi**, and **28aj–bj** which contain a piperazinyl linker have a more pronounced quinolone-type antibacterial spectrum (i.e., potent activ-

Table 2
In vitro antibacterial activity of quinolone-substituted 8a-azaketolides (**28ah–am** and **28bh–bm**)[a,b]

Compound	*S. aureus*				*S. pneumoniae*			*S. pyogenes*				*M. catarrhalis*	*H. influenzae*
	B0329 Ery-S	B0538 iMLS	B0330 cMLS	B0331 M	B0541 Ery-S	B0627 cMLS	B0326 M	B0542 Ery-S	B0543 iMLS	B0544 cMLS	B0545 M	B0324	B0529
28ah–bh	1	1	>64	0.25	⩽0.125	1	0.25	⩽0.125	1	4	0.5	⩽0.125	1
28ai	⩽0.125	0.25	2	0.25	⩽0.125	⩽0.125	⩽0.125	⩽0.125	⩽0.125	2	0.5	⩽0.125	⩽0.125
28bi	⩽0.125	0.25	8	0.5	⩽0.125	0.5	0.25	⩽0.125	0.5	4	0.5	0.5	0.25
28aj–bj	0.25	0.25	>64	2	⩽0.125	1	0.5	⩽0.125	0.25	4	2	1	2
28ak–bk	1	2	>64	0.5	⩽0.125	4	1	⩽0.125	4	32	4	4	8
28al–bl	1	1	>64	4	⩽0.125	2	2	⩽0.125	1	8	16	2	2
28am–bm	4	>64	>64	32	0.125	>64	0.25	0.125	>64	>64	16	0.5	4
40	0.125	16	⩽0.125	⩽0.125	⩽0.125	0.25	0.25	2	0.25	0.5	⩽0.125	0.125	⩽0.125
Azi	1	>64	>64	>64	⩽0.125	>64	4	⩽0.125	8	>64	1	0.25	1
2	⩽0.125	0.5	>64	0.25	⩽0.06	⩽0.125	0.5	⩽0.06	⩽0.06	4	0.25	⩽0.125	2
3	⩽0.06	0.25	>64	0.25	⩽0.06	⩽0.125	⩽0.06	⩽0.06	⩽0.06	1	⩽0.125	⩽0.125	2

Ery-S, erythromycin-susceptible strains; iMLS, inducibly-resistant strains; cMLS, constitutively-resistant strains; M, efflux-resistant strains; Azi, azithromycin.
[a] Minimum inhibitory concentration (MIC) values are given in μg/mL.
[b] All the compounds among the β-amino alcohol series except **28ai** and **28bi** were tested as diastereoisomeric mixtures.

ity against Gram-negative bacteria, especially *H. influenzae* and *M. catarrhalis* strains such as B0529 and B0324). Ketolides **28ai** and **28bi**, with a 'cyprofloxacin-like' moiety substituted at the C-6 position of the 8a-azaketolide core, exhibited potent antibacterial activity against constitutively MLS_B-resistant *S. pneumoniae* and *S. pyogenes*. Most importantly, these compounds also showed an outstanding activity against constitutively MLS_B-resistant *S. aureus* and *H. influenzae*. Other analogues within the same series, with benzene, pyridine, and quinoline rings (e.g., **28aa–ba**, **28ab–bb**, **28ac–bc**, **28ad–bd**, and **28af–bf**, see Table 1) were ca. 20–30-fold less active than **28ai** against a panel of representative erythromycin-sensitive and erythromycin-resistant strains. Thus, it seems that a quinolone moiety attached to the ketolide core is a requirement for potent antibacterial activity.

From the above structure–activity relationships we have identified three important structural features that contribute to improvement of the antibacterial activity within the macrolide-quinolone subgroup of ketolides: (a) the presence of the carboxylic acid at the C-3 position of quinolone moiety, (b) the presence of a tether at the C-7 position and fluoro substituent at the C-6 position, and (c) the introduction of a supplementary basic site, such as amino group in the 6-*O*-propyl side chain of ketolides was beneficial for the activity against *H. influenzae*. Esterification of the carboxyl group at the C-3 position of **28ai** dramatically reduced antibacterial activity confirming the key role generally played by this portion of the molecule in the biological activity of quinolones.[22]

Analogues **28ah–bh**, **28ai–bi**, and **28aj–bj** were active against strains inducibly and constitutively resistant to erythromycin A, with MICs versus the MLS_B-resistant *S. pneumoniae* and the efflux-resistant *S. pneumoniae* (B0326) in the range of 0.125–1 and 0.125–0.5 μg/mL, respectively. Similar results were found for *S. pyogenes* strains, both inducibly and constitutively resistant to erythromycin A. Therefore, macrolide-quinolone hybrids **28ah–bh**, **28ai**, **28bi**, and **28aj–bj** were ca. 8–64-fold more active than azithromycin against both, inducibly and constitutively MLS_B-resistant *S. pyogenes*. Furthermore, macrolide-quinolone hybrids **28ai** and **28bi** were 2–8-fold more active than azithromycin against two important Gram-negative respiratory tract pathogens, *H. influenzae* and *M. catarrhalis*. Actually, these compounds were as active versus latter strains as the parent quinolone, ciprofloxacin (**40**). In agreement with the quinolone SAR, the activity of ester **28am–bm** (mixture of *syn*- and *anti*-isomers) is inferior to that of the corresponding acid (*syn*-**28ai** and *anti*-**28bi**). Attenuated activity of the 'ciprofloxacin-like' hybrids **28ai** and **28bi** against Gram-negative respiratory pathogens, *H. influenzae* and *M. catarrhalis*, is suggestive of an enhanced contribution of the quinolone mode of action in these analogues versus an azaketolide prevailing mode of action in ethylenediamine-linked analogues **28ak–bk** and **28al–bl**.[§]

The structure–activity studies described in this paper have uncovered new types of ketolide-quinolone hybrid antibiotics, which displayed high levels of antibacterial activity. These studies indicated that a quinolone component was essential for strong antimicrobial activity and that the nature of the linker connecting the ketolide and quinolone substructures was as equally important for potent activity. A striking difference in the antimicrobial spectrum of **28ai** and **28al–bl** can best be explained by the different molecular shape induced by the nature of the different linkers. Compound **28ai**, which possesses a piperazinyl linker, displayed an antimicrobial spectrum similar to ciprofloxacin (i.e., potent activity against Gram-negative pathogens and reduced activity against erythromycin-resistant Gram-positive pathogens, especially against constitutively MLS_B-resistant *S. pyogenes*).[23] In contrast, compounds **28al–bl**, which contain an ethylenediamino linker, have more pronounced azaketolide type antimicrobial spectrum (i.e., potent activity against Gram-positive pathogens and reduced activity against Gram-negative pathogens).[24]

3. Conclusion

A series of ketolide-quinolone hybrid antibacterials has been discovered. Their in vitro antibacterial activity encompasses a large variety of clinically relevant susceptible as well as MLS_B-resistant (i.e., *erm*(B) *S. pneumoniae*, *mef*(A) *S. pneumoniae*, *erm*(B) *S. pyogenes*) Gram-positive and fastidious Gram-negative bacteria. Most notably they were active against constitutively MLS_B-resistant *S. aureus*, and showed excellent in vitro activity against *H. influenzae* and *M. catarrhalis*. The ketolide-ciprofloxacin hybrids **28ai** and **28bi** were found to display high antibacterial activity against the constitutively-resistant strains of *S. pneumoniae* and *S. pyogenes* and significantly potent activity against the constitutively MLS_B-resistant *S. aureus*, *H. influeanzae*, and *M. catarrhalis*.

[§] We believe that the enhanced potency and expanded antibacterial spectrum of new macrolide-quinolone hybrids are consistent with anticipated dual macrolide/quinolone mode of action. Furthermore, due to balanced dual mode of action the best representatives overcome all types of resistance in clinically important gram-positive pathogens. However, additional experiments using standard protein inhibition and DNA gyrase gel-based supercoil assays are needed to give definitive evidence on the mode of action of hybrids.

4. Experimental section

4.1. General experimental methods

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectra were recorded on either a Bruker 300 or a Bruker 500 MHz spectrometer. Chemical shifts were recorded in parts per million (δ) relative to tetramethylsilane (δ 0.00). Low-resolution electron impact mass spectra (MS) were recorded on a Varian MAT CH5 spectrometer. Fast atom bombardment (FAB) mass spectra were run on a Finnigan MAT 312 double focusing mass spectrometer, operating at an accelerating voltage of 3 kV. The samples were ionized by bombardment with xenon atoms produced by a saddle-field ion source from Ion Tech operating with a tube current of 2 mA at energy of 6 keV. Electrospray positive ion mass spectra were acquired using a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer, equipped with a Z-spray interface, over a mass range of 100–2000 Da, with a scan time of 1.5 s and an interscan delay of 0.1 s in a continuum mode. Reserpine was used as the external mass calibrant lock mass ($[M+H]^+$ = 609.2812 Da). The elemental composition was calculated using a MassLynx v4.1 for the $[M+H]^+$ and the mass error quoted within ±5 ppm range. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F254 0.2-mm plates. The plates were visualized by using an acid-based stain, prepared from *p*-anisaldehyde (5 mL), concentrated sulfuric acid (5 mL), and glacial acetic acid (0.5 mL) in 95% ethanol (90 mL) and warming on a hot plate. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). Solvent systems are reported as volume percent mixtures. Concentration in vacuo refers to the removal of solvent using a Büchi rotary evaporator and an aspirator pump. All chromatography solvents were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from calcium hydride. All other reagents were purified by literature procedures. All reactions were performed under an inert atmosphere of dry argon. The course of the reaction was followed by chromatography on a thin layer (TLC) of silica gel (Merck 60 F_{254}) in solvent systems methylene chloride/methanol/ammonium hydroxide 25% (90:9:1.5, system A), (90:9:0.5), system A1) or methylene chloride/acetone (8:2, system B) (7:3, System C) unless otherwise stated. The separation of the reaction products and the purification of the products for the purpose of spectral analyses were performed on a silica gel column (Merck 60, 230–400 mesh, or 60–230 mesh in solvent systems A, B, or C unless otherwise stated.

4.2. Experimental procedures

4.2.1. Beckmann rearrangement of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)- and 9(*Z*)-oximes (7 and 8). Preparation of 3-*O*-descladinosyl-6-*O*-allyl-8a-aza-8a-homoerythromycin A[9] (9) and 3-*O*-descladinosyl-6-*O*-allyl-9a-aza-9a-homoerythromycin A (10)

The corresponding oxime (1.20 g, 1.9 mmoL) was dissolved in acetone (50 mL) and the solution was cooled to 0–5 °C in an ice-bath. Subsequently, the solutions of *p*-toluenesulfonylchloride (1.84 g, 14.0 mmoL) in acetone (56 mL) and sodium hydrogen carbonate (1.16 g, 14.0 mmoL) in water (180 mL) were simultaneously added thereto within 1 h under stirring. The reaction mixture was stirred at room temperature for an additional 2 h, acetone was evaporated at reduced pressure, and the aqueous layer was washed with chloroform (70 mL). The pH of the aqueous layer was adjusted to 9.0 with 2 M aq NaOH and extracted twice with chloroform (2 × 70 mL). The combined organic extracts at pH 9.0 were dried over K_2CO_3 and evaporated in vacuo, yielding the crude rearranged product, which was purified by chromatography on a silica gel column using methylene chloride/methanol/concd ammonium hydroxide (90:9:1.5) as eluent to give the following descladinosyl lactams as colorless solids.

4.2.1.1. 3-*O*-Descladinosyl-6-*O*-allyl-8a-aza-8a-homoerythromycin A (9). 1.1 g of **9** (90%) was obtained by the above procedure from 1.2 g of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*Z*)-oxime (**8**). FAB-MS *m*/*z* 631 (MH^+, 100%); ^{1}H NMR ($CDCl_3$) δ 6.03 (1H, 8a-CO*NH*), 5.96 (1H, 6-OCH$_2$*C*HCH$_2$), 5.28 (1H, 6-OCH$_2$CHC*H*$_{2b}$), 5.15 (1H, 6-OCH$_2$CHC*H*$_{2a}$), 5.01 (1H, H-13), 4.52 (1H, H-1′), 3.93 (2H, 6-O*C*H$_2$CHCH$_2$), 3.82 (1H, H-8), 3.78 (1H, H-3), 3.73 (1H, H-5), 3.56 (1H, H-5′), 3.39 (1H, H-11), 3.28 (1H, H-2′), 2.69 (1H, H-3′), 2.64 (1H, H-2), 2.45 (1H, H-10), 2.37 (6H, 3′-NMe$_2$), 2.24 (1H, H-7b), 2.14 (1H, H-4), 1.91 (1H, H-14b), 1.75 (1H, H-4′b), 1.57–1.46 (2H, H-14a, H-7a), 1.39 (3H, 6-Me), 1.32 (3H, 8-Me), 1.31 (3H, 2-Me), 1.29 (1H, H-4′a), 1.25 (3H, 5′-Me), 1.19 (3H, 10-Me), 1.13 (3H, 12-Me), 1.11 (3H, 4-Me), 0.88 (3H, 15-Me); ^{13}C NMR ($CDCl_3$) δ 176.4 (s, C-1), 174.8 (s, 8a-*C*ONH), 136.0 (d, 6-OCH$_2$*C*HCH$_2$), 116.1 (t, 6-OCH$_2$CHC*H*$_2$), 105.9 (d, C-1′), 89.5 (d, C-5), 78.5 (s, C-6), 78.1 (d, C-3), 76.4 (d, C-13), 74.9 (s, C-12), 70.6 (d, C-11), 70.1 (d, C-2′), 69.5 (d, C-5′), 65.4 (d, C-3′), 63.4 (t, 6-O*C*H$_2$CHCH$_2$), 43.8 (d, C-2), 43.1 (d, C-8), 42.9 (d, C-10), 41.6 (t, C-7), 39.9 (q, 3′-NMe$_2$), 35.6 (d, C-4), 28.0 (t, C-4′), 22.4 (q, 8-Me), 21.8 (q, 6-Me), 21.1 (t, C-14), 20.8 (q, 5′-Me), 16.2 (q, 12-Me), 15.7 (q, 2-Me), 10.5 (q, 15-Me), 10.3 (q, 10-Me), 8.0 (q, 4-Me). Anal. Calcd for $C_{32}H_{58}N_2O_{10}$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.75; H, 9.53; N, 4.32.

4.2.1.2. 3-*O*-Descladinosyl-6-*O*-allyl-9a-aza-9a-homoerythromycin A (10). 1.03 g of **10** (86%) was obtained by the above procedure from 1.2 g of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime (**7**). FAB-MS *m*/*z* 631 (MH^+, 100%); ^{1}H NMR ($CDCl_3$) δ 6.97 (1H, 9a-CO*NH*), 6.00 (1H, 6-OCH$_2$*C*HCH$_2$), 5.34 (1H, 6-OCH$_2$CHC*H*$_{2b}$), 5.23 (1H, 6-OCH$_2$CHC*H*$_{2a}$), 4.64 (1H, H-13), 4.58 (1H, H-1′), 4.13 (1H, H-10), 4.07 (1H, 6-O*C*H$_{2b}$CHCH$_2$), 3.97 (1H, 6-O*C*H$_{2a}$CHCH$_2$), 3.79 (1H, H-5), 3.75 (1H, H-3), 3.57 (1H, H-5′), 3.27 (1H, H-2′), 3.13 (1H, H-11), 2.71–2.60 (2H, H-3′, H-2), 2.48 (1H, H-8), 2.35 (6H, 3′-NMe$_2$), 2.11 (1H, H-4), 1.90 (1H, H-14b), 1.82 (1H, H-7b), 1.73 (1H, H-4′b), 1.57 (1H, H-14a), 1.44 (1H, H-7a), 1.39 (3H, 6-Me), 1.32 (3H, 2-Me), 1.29 (1H, H-4′a), 1.26 (3H, 5′-Me), 1.18 (3H, 10-Me), 1.12 (3H, 8-Me), 1.11 (3H, 12-Me), 1.00 (3H, 4-Me), 0.90 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 178.9 (s, C-1), 176.9 (s, 9a-*C*ONH), 135.1 (d, 6-OCH$_2$*C*HCH$_2$), 117.6 (t, 6-OCH$_2$CHC*H*$_2$), 106.2 (d, C-1′), 88.7 (d, C-5), 80.0 (s, C-6), 78.9 (d, C-13), 78.2 (d, C-3), 74.1 (d, C-11; s, C-12; 2C), 70.2 (d, C-2′), 69.6 (d, C-5′), 65.8 (d, C-3′), 64.1 (t, 6-O*C*H$_2$CHCH$_2$), 45.9 (d, C-10), 44.1 (d, C-2), 41.5 (t, C-7), 40.1 (q, 3′-NMe$_2$), 35.8 (d, C-4), 32.9 (d, C-8), 28.4 (t, C-4′), 21.0 (q, 5′-Me), 20.8 (t, C-14), 19.2 (q, 6-Me), 17.4 (q, 8-Me), 16.1 (q, 2-Me), 15.9 (q, 12-Me), 15.3 (q, 10-Me), 10.9 (q, 15-Me), 7.8 (q, 4-Me). HRMS (ES) calcd for $C_{32}H_{58}N_2O_{10}$ (MH^+) 631.4091, found 631.4071. Anal. Calcd for $C_{32}H_{58}N_2O_{10}$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.80; H, 9.48; N, 4.30.

4.2.2. Beckmann rearrangement of 3-*O*-descladinosyl-6,12-di-*O*-allylerythromycin A 9(*E*)-oxime (12). Preparation of 3-*O*-descladinosyl-6,12-di-*O*-allyl-9a-aza-9a-homoerythromycin A (13)

To a solution of the oxime **12** (15.86 g, 23.6 mmoL) in acetone (200 mL) were simultaneously added a solution of *p*-TsCl (20.8 g, 0.14 moL) in acetone (340 mL) and a solution of $NaHCO_3$ (20.5 g, 0.28 moL) in water (340 mL) over a period of 1 h at a rate to keep the internal temperature below 5 °C. The reaction mixture was stirred for an additional 2 h and then allowed to warm to room temperature overnight. Acetone was evaporated in vacuo, the

aqueous layer was made basic (pH 9.0) with 2 M aqueous NaOH, and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were dried over K_2CO_3 and evaporated in vacuo to give the crude lactam as a faintly yellow solid, which, if appropriate, was purified by chromatography on a silica gel column using methylene chloride/methanol/concd ammonium hydroxide (90:9:1.5) as eluent to give 9a-lactam **13** as a colorless solid: 11.42 g (72%) was prepared by the above procedure from 15.86 g of 3-*O*-descladinosyl-6,12-di-*O*-allylerythromycin A 9(*E*)-oxime (**12**). FAB-MS *m*/*z* 671 (MH^+, 76%); ^1H NMR ($CDCl_3$) δ 6.97 (1H, 9a-CO*NH*), 6.00 (1H, 6-OCH$_2$*CH*CH$_2$), 5.83 (1H, 12-OCH$_2$*CH*CH$_2$), 5.32 (1H, 6-OCH$_2$CH*CH$_{2b}$*), 5.28 (1H, H-13), 5.22 (1H, 12-OCH$_2$CH*CH$_{2a}$*), 5.21 (1H, 6-OCH$_2$CH*CH$_{2a}$*), 5.09 (1H, 12-OCH$_2$CH*CH$_{2a}$*), 4.64 (1H, H-1′), 4.47 (1H, 12-O*CH$_{2b}$*CHCH$_2$), 4.23 (1H, H-10), 4.17 (1H, 3-OH), 4.03 (1H, 6-O*CH$_{2b}$*CHCH$_2$), 4.00 (1H, 12-O*CH$_{2a}$*CHCH$_2$), 3.92 (1H, 6-O*CH$_{2a}$*CHCH$_2$), 3.79 (1H, H-5), 3.71 (1H, H-3), 3.59 (1H, H-5′), 3.29 (1H, H-2′), 3.15 (1H, H-11), 2.75 (1H, H-3′), 2.66 (1H, H-2), 2.45 (1H, H-8), 2.40 (6H, 3′-NMe$_2$), 2.08 (1H, H-4), 1.80 (1H, H-7b), 1.76 (1H, H-14b), 1.74 (1H, H-4′a), 1.64 (1H, H-14a), 1.42 (1H, H-7a), 1.38 (3H, 6-Me), 1.32 (3H, 2-Me), 1.29 (1H, H-4′a), 1.26 (3H, 5′-Me), 1.22 (3H, 10-Me), 1.15 (3H, 12-Me), 1.12 (3H, 8-Me), 1.00 (3H, 4-Me), 0.93 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 178.3 (s, C-1), 176.7 (s, C-9), 134.93 (d, 6-OCH$_2$*CH*CH$_2$), 134.90 (d, 12-OCH$_2$*CH*CH$_2$), 117.8 (t, 6-OCH$_2$CH*CH$_2$*), 115.9 (t, 12-OCH$_2$CH*CH$_2$*), 106.0 (d, C-1′), 88.8 (d, C-5), 79.9 (s, C-6), 78.3 (d, C-3), 78.1 (s, C-12), 77.4 (d, C-11), 76.3 (d, C-13), 70.2 (d, C-2′), 69.4 (d, C-5′), 66.0 (d, C-3′), 65.6 (t, 12-O*CH$_2$*), 64.2 (t, 6-O*CH$_2$*), 45.7 (d, C-10), 44.3 (d, C-2), 41.4 (t, C-7), 40.2 (q, 3′-NMe$_2$), 35.7 (d, C-4), 33.0 (d, C-8), 28.7 (t, C-4′), 21.0 (q, 5′-Me), 20.8 (t, C-14), 19.2 (q, 6-Me), 17.5 (q, 8-Me), 16.8 (q, 12-Me), 16.0 (q, 2-Me), 15.3 (q, 10-Me), 10.6 (q, 15-Me), 7.9 (q, 4-Me). HRMS (ES) calcd for $C_{35}H_{62}N_2O_{10}$ (MH^+) 671.4404, found 671.4385. Anal. Calcd for $C_{35}H_{62}N_2O_{10}$: C, 62.66; H, 9.32; N, 4.18. Found: C, 62.51; H, 9.50; N, 4.22.

4.2.3. General procedure for the preparation of 3-*O*-descladinosyl-3-oxy-6-*O*-allyl-8a-aza-8a-homoerythromycin A 2′-*O*-acetate[9] (14) and 3-*O*-descladinosyl-3-oxy-6-*O*-allyl-9a-aza-9a-homoerythromycin A 2′-*O*-acetate (15)

To a solution of the corresponding homoerythromycin A derivative (757.0 mg, 1.2 mmoL) in methylene chloride (25 mL), triethylamine (141.7 mg, 1.4 mmoL) and acetic acid anhydride (0.128 mL, 1.3 mmoL) were added and the reaction mixture was stirred for 3 h at room temperature. Following addition of the saturated solution of sodium hydrogen carbonate (30 mL), the layers were separated and the aqueous portion was additionally extracted with methylene chloride (2 × 20 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (30 mL) and water (30 mL), dried over K_2CO_3, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/acetone; 50:50) to furnish the corresponding 2′-*O*-acetyl derivatives as colorless solids.

4.2.3.1. 3-*O*-Decladinosyl-3-oxy-6-*O*-allyl-8a-aza-8a-homoerythromycin A 2′-*O*-acetate (14). 726.8 mg (90%) was obtained by the above procedure from 757 mg of 3-decladinosyl-3-oxy-6-*O*-allyl-8a-aza-8a-homoerythromycin A (9). MS (ES) *m*/*z* 673 (MH^+, 87%).

4.2.3.2. 3-*O*-Decladinosyl-3-oxy-6-*O*-allyl-9a-aza-9a-homoerythromycin A 2′-*O*-acetate (15). 702.6 mg (87%) was prepared by the above procedure from 757 mg of 3-decladinosyl-3-oxy-6-*O*-allyl-9a-aza-9a-homoerythromycin A (**10**). MS (ES) *m*/*z* 673 (MH^+, 52%).

4.2.4. Dess–Martin oxidation. Preparation of 3-*O*-descladinosyl-3-oxo-6-*O*-allyl-8a-aza-8a-homoerythromycin A[9] (18) and 3-*O*-descladinosyl-3-oxo-6-*O*-allyl-9a-aza-9a-homoerythromycin A (19)

To a solution of the corresponding 2′-*O*-acetyl derivative (1.48 g, 2.2 mmoL) in methylene chloride (5 mL) was added $NaHCO_3$ (10.0 equiv), pyridine (5.0 equiv), and Dess–Martin reagent (2.0 equiv), and the reaction was stirred for 3 h at ambient temperature. The reaction was quenched by consecutive addition of saturated $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ $5H_2O$ (1.17 g, 4.7 mmoL, 13.9 equiv). The resulting solution was stirred for an additional 30 min, extracted with methylene chloride (2 × 25 mL), dried over K_2CO_3, and concentrated in vacuo. This crude residue was then dissolved in MeOH (20.0 mL) and refluxed for 3 h. After evaporation of the solvent, the residue was taken up in water, the pH adjusted to 11 with 2 M aqueous sodium hydroxide, and the mixture extracted with ethyl acetate. The extracts were washed with water, dried over K_2CO_3, and evaporated to dryness. The product was purified by column chromatography eluting with acetone/hexane/aq NH_3 (50:50:0.5) solvent system to afford the following compounds as pale yellow solids.

4.2.4.1. 3-*O*-Descladinosyl-3-oxo-6-*O*-allyl-8a-aza-8a-homoerythromycin A (18). FAB-MS *m*/*z* 629 (MH^+, 89%); ^1H NMR ($CDCl_3$) δ 6.17 (1H, 8a-CO*NH*), 5.89 (1H, 6-OCH$_2$*CH*CH$_2$), 5.18 (1H, 6-OCH$_2$CH*CH$_{2b}$*), 5.15 (1H, 6-OCH$_2$CH*CH$_{2a}$*), 5.09 (1H, H-13), 4.31 (1H, H-5), 4.25 (1H, H-1′), 3.94 (1H, H-8), 3.80 (1H, H-2), 3.73 (2H, 6-O*CH$_2$*CHCH$_2$), 3.60 (1H, H-5′), 3.55 (1H, H-11), 3.22 (1H, H-2′), 3.11 (1H, H-4), 2.62 (1H, H-3′), 2.44 (1H, H-10), 2.36 (6H, 3′-NMe$_2$), 1.98–1.93 (2H, H-14b, H-7b), 1.77 (1H, H-4′a), 1.61 (1H, H-7a), 1.52 (1H, H-14a), 1.37 (3H, 2-Me), 1.34 (3H, 4-Me), 1.26 (3H, 6-Me), 1.24 (3H, 5′-Me), 1.19 (3H, 8-Me), 1.18 (3H, 12-Me), 0.88 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 206.2 (s, C-3), 174.4 (s, C-9), 170.5 (s, C-1), 136.8 (d, 6-OCH$_2$*CH*CH$_2$), 115.6 (t, 6-OCH$_2$CH*CH$_2$*), 102.6 (d, C-1′), 78.8 (s, C-6), 77.8 (d, C-5), 77.6 (d, C-13), 74.3 (s, C-12), 70.7 (d, C-11), 69.9 (d, C-2′), 69.0 (d, C-5′), 65.6 (d, C-3′), 64.0 (t, 6-O*CH$_2$*CHCH$_2$), 49.9 (d, C-2), 46.9 (d, C-4), 42.5 (d, C-8), 42.2 (d, C-10), 41.9 (t, C-7), 40.0 (q, 3′-NMe$_2$), 28.6 (t, C-4′), 22.7 (q, 8-Me), 22.1 (q, 6-Me), 21.2 (t, C-14), 20.9 (q, 5′-Me), 16.0 (q, 12-Me), 14.6 (q, 4-Me), 13.9 (q, 2-Me), 10.5 (q, 15-Me), 9.7 (q, 10-Me). Anal. Calcd for $C_{32}H_{56}N_2O_{10}$: C, 61.12; H, 8.98; N, 4.45. Found: C, 61.47; H, 9.28; N, 4.38.

4.2.4.2. 3-*O*-Descladinosyl-3-oxo-6-*O*-allyl-9a-aza-9a-homoerythromycin A (19). FAB-MS *m*/*z* 629 (MH^+, 100%); ^1H NMR ($CDCl_3$) δ 6.62 (1H, 9a-CO*NH*), 5.92 (1H, 6-OCH$_2$*CH*CH$_2$), 5.28 (1H, 6-OCH$_2$CH*CH$_{2b}$*), 5.17 (1H, 6-OCH$_2$CH*CH$_{2a}$*), 4.68 (1H, H-13), 4.50 (1H, H-5), 4.43 (1H, H-1′), 4.14 (1H, H-10), 3.96 (1H, 6-O*CH$_{2b}$*CHCH$_2$), 3.89 (1H, H-2), 3.73 (1H, 6-O*CH$_{2a}$*CHCH$_2$), 3.41 (1H, H-2′), 3.28 (1H, H-11), 3.07 (1H, H-4), 2.95 (1H, H-3′), 2.61 (6H, 3′-NMe$_2$), 2.43 (1H, H-8), 2.05 (1H, H-4′b), 1.98–1.86 (2H, H-14a, H-7b), 1.61 (1H, H-14a), 1.46 (1H, H-7a), 1.41 (1H, H-4′a), 1.39 (3H, 2-Me), 1.32 (3H, 6-Me), 1.31 (3H, 5′-Me), 1.29 (3H, 4-Me), 1.19 (3H, 12-Me), 1.18 (3H, 10-Me), 1.13 (3H, 8-Me), 0.91 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 206.7 (s, C-3), 176.9 (s, C-9), 174.1 (s, C-1), 136.1 (d, 6-OCH$_2$*CH*CH$_2$), 117.2 (t, 6-OCH$_2$CH*CH$_2$*), 101.8 (d, C-1′), 79.8 (d, C-13), 79.5 (s, C-6), 74.9 (d, C-5), 74.2 (s, C-12), 73.4 (d, C-11), 70.0 (d, C-2′), 68.7 (d, C-5′), 66.0 (d, C-3′), 63.9 (t, 6-O*CH$_2$*CHCH$_2$), 49.2 (d, C-2), 46.1 (d, C-4), 45.9 (d, C-10), 41.1 (t, C-7), 40.5 (q, 3′-NMe$_2$), 34.2 (d, C-8), 30.7 (t, C-4′), 21.1 (q, 6-Me), 20.8 (t, C-14), 20.3 (q, 5′-Me), 18.6 (q, 8-Me), 16.1 (q, 12-Me), 14.7 (q, 10-Me), 14.3 (q, 4-Me), 13.9 (q, 2-Me), 11.1 (q, 15-Me). HRMS (ES) calcd for $C_{32}H_{56}N_2O_{10}$ (MH^+) 629.3935, found 629.3913. Anal. Calcd for $C_{32}H_{56}N_2O_{10}$: C, 61.12; H, 8.98; N, 4.45. Found: C, 61.40; H, 9.23; N, 4.40.

4.2.5. Pfitzner–Moffat oxidation of 2′-*O*-acetyl-3-*O*-descladinosyl-6,12-di-*O*-allyl-9a-aza-9a-homoerythromycin A (20). Preparation of 3-*O*-descladinosyl-6,12-di-*O*-allyl-3-oxo-9a-aza-9a-homoerythromycin A (22)

To a solution of 2′-*O*-acetyl derivative **20** prepared according to standard procedure (1.48 g, 2.2 mmoL), EDC HCl (2.70 g, 14.0 mmoL), and DMSO (2.5 mL, 35.2 mmoL) in 20 mL of methylene chloride was added dropwise at 0 °C a solution of pyridinium trifluoroacetate (2.70 g, 14.0 mmoL) in 5 mL of methylene chloride. The reaction was stirred 5 h at room temperature, and 10 mL of water was added. After stirring for 10 min, the mixture was taken up in 50 mL of methylene chloride, followed by washing with water, drying over $MgSO_4$, and evaporation of the solvent. The oily residue was dissolved in MeOH (20.0 mL) and refluxed for 3 h. After evaporation of the solvent, the residue was taken up in water, the pH adjusted to 11 with 2 M aqueous sodium hydroxide, and the mixture extracted with ethyl acetate. The extracts were washed with water, dried over K_2CO_3, and evaporated to dryness. The product was purified by column chromatography eluting with acetone/hexane/aq NH_3 (50:50:0.5) solvent system to afford ketolide **22** as pale yellow solid: FAB-MS *m*/*z* 669 (MH^+, 63%); ^{1}H NMR ($CDCl_3$) δ 7.49 (1H, 9a-CO*NH*), 5.94 (1H, 6-OCH$_2$*CH*CH$_2$), 5.91 (1H, 12-OCH$_2$*CH*CH$_2$), 5.34 (1H, 12-OCH$_2$CH*CH*$_{2b}$), 5.26 (1H, 6-OCH$_2$CH*CH*$_{2b}$), 5.20 (1H, 12-OCH$_2$CH*CH*$_{2a}$), 5.14 (1H, 6-OCH$_2$CH*CH*$_{2a}$), 4.99 (1H, H-13), 4.64 (1H, H-5), 4.53 (1H, H-10), 4.34 (1H, H-1′), 4.06 (2H, 12-O*CH*$_{2b}$), 3.94 (2H, 12-O*CH*$_{2a}$), 3.90 (2H, 6-O*CH*$_{2b}$), 3.78 (2H, 6-O*CH*$_{2a}$), 3.75 (1H, H-2), 3.67 (1H, H-5′), 3.47 (1H, H-2′), 3.36 (1H, H-4), 3.02 (1H, H-3′), 2.68 (6H, 3′-NMe$_2$), 2.63 (1H, H-8), 2.59 (1H, H-7b), 2.24 (1H, H-4′b), 1.96 (1H, H-14b), 1.69 (3H, 10-Me), 1.56 (1H, H-14a), 1.45 (1H, H-4′a), 1.39 (3H, 12-Me), 1.38 (3H, 4-Me), 1.37 (1H, H-7a), 1.34 (3H, 6-Me), 1.32 (3H, 2-Me), 1.31 (3H, 5′-Me), 1.12 (3H, 8-Me), 0.90 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 207.7 (s, C-3), 178.0 (s, C-9), 172.0 (s, C-1), 135.0 (d, 6-OCH$_2$*CH*CH$_2$), 133.9 (d, 12-OCH$_2$*CH*CH$_2$), 117.8 (t, 6-OCH$_2$CH*CH*$_2$), 116.9 (t, 12-OCH$_2$CH*CH*$_2$), 101.9 (d, C-1′), 85.1 (s, C-12), 80.3 (s, C-6), 76.0 (d, C-13), 74.5 (d, C-5), 70.2 (d, C-2′), 68.6 (d, C-5′), 66.7 (t, 12-O*CH*$_2$), 65.9 (d, C-3′), 63.9 (t, 6-O*CH*$_2$), 54.6 (d, C-10), 48.7 (d, C-2), 44.8 (d, C-4), 39.9 (t, C-7), 32.8 (d, C-8), 31.9 (t, C-4′), 21.1 (t, C-14), 21.0 (q, 5′-Me), 19.6 (q, 6-Me), 17.9 (q, 8-Me), 16.4 (q, 10-Me), 14.8 (q, 12-Me, 4-Me, 2C), 13.4 (q, 2-Me), 10.5 (q, 15-Me). HRMS (ES) calcd for $C_{35}H_{60}N_2O_{10}$ (MH^+) 669.4248, found 669.4230. Anal. Calcd for $C_{35}H_{60}N_2O_{10}$: C, 62.85; H, 9.04; N, 4.19. Found: C, 62.56; H, 9.29; N, 4.03.

4.2.6. General procedure for the synthesis of 8a-aza and 9a-aza homoerythromycin ketolides (23–24a–c)

4.2.6.1. Preparation of 3-oxo-6-*O*-[3-(1′-naphthyl)-2-propenyl]-8a-aza-8a-homoerythromycin A (23a). To a solution of 3-oxo-6-*O*-allyl-8a-aza-8a-homoerythromycin A (**18**, 1.0 g, 1.59 mmoL), palladium(II) acetate (67 mg, 0.30 mmoL), and tri(*o*-tolyl)phosphine (181 mg, 0.60 mmoL) in dry acetonitrile (7 mL) were added 1-iodonaphthalene (0.65 mL, 4.47 mmoL) and triethylamine (0.83 mL, 5.96 mmoL), and the mixture was stirred under argon for 30 min. The reaction mixture was warmed to 60 °C for 2 h and stirred at 90 °C for 20 h. The reaction mixture was taken up in ethyl acetate, washed twice aqueous 5% sodium bicarbonate, once with aqueous 2% tris(hydroxymethyl)aminomethane, and once with brine, dried over sodium sulfate, filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (95:5:0.5 CH_2Cl_2/MeOH/aq NH_3) to give **23a** (866 mg, 72%) as a colorless solid: FAB-MS *m*/*z* 755 (MH^+, 89%); ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1H), 7.96 (d, 1H), 7.93 (d, 1H), 7.78 (d, 1H), 7.55 (m, 2H), 7.50 (m, 1H), 6.65 (d, 1H), 6.25 (m, 1H), 4.05 (dd, 2H), 3.36 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 211.3, 179.6, 172.0, 135.6, 133.5, 132.0, 129.1, 128.8, 128.3, 126.9, 126.5, 126.3, 126.0, 124.0, 122.9, 69.4, 51.6. HRMS (ES) calcd for $C_{42}H_{62}N_2O_{10}$ (MH^+) 755.4404, found 755.4390. Anal. Calcd for $C_{42}H_{62}N_2O_{10}$: C, 66.82; H, 8.28; N, 3.71. Found: C, 67.05; H, 8.59; N, 3.40.

The following compounds were prepared by using the same experimental procedure.

4.2.6.2. 3-Oxo-6-*O*-[3-(3′-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A (23b). FAB-MS *m*/*z* 756 (MH^+, 83%); ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 8.38 (d, 1H), 8.06 (d, 1H), 7.98 (d, 1H), 7.78 (m, 1H), 7.60 (m, 1H) 6.56 (1H, 6-OCH$_2$CH*CH*Q), 6.32(1H, 6-OCH$_2$*CH*CHQ) 6.19 (1H, 8a-CO*NH*), 5.08 (1H, H-13), 4.28 (1H, H-5), 4.16 (1H, H-1′), 3.85 (1H, H-2), 3.81 (2H, 6-O*CH*$_2$CHCHQ), 2.40 (6H, 3′-NMe$_2$), 1.38 (3H, 2-Me), 0.91 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 205.9 (s, C-3), 175.6 (s, C-9), 171.8 (s, C-1), 149.3, 147.9, 135.9, 129.7, 128.5, 128.4, 128.3, 127.6, 127.2 (6-OCH$_2$CHCHQ), 132.5 (d, 6-OCH$_2$CH*CH*Q), 129.1 (d, 6-OCH$_2$*CH*CHQ), 101.7 (d, C-1′), 64.0 (t, 6-O*CH*$_2$CHCHQ), 49.0 (d, C-2), 13.4 (q, 2-Me), 10.8 (q, 15-Me). HRMS (ES) calcd for $C_{41}H_{61}N_3O_{10}$ (MH^+) 756.4357, found 756.4345. Anal. Calcd for $C_{41}H_{61}N_3O_{10}$: C, 65.14; H, 8.13; N, 5.56. Found: C, 65.23; H, 8.23; N, 5.40.

4.2.6.3. 3-Oxo-6-*O*-[3-(4′-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A (23c). FAB-MS *m*/*z* 756 (MH^+, 91%); ^{1}H NMR ($CDCl_3$) δ 8.79 (d, 1H), 7.98 (d, 1H), 7.78 (m, 1H), 7.60 (m, 1H), 7.32 (d, 1H), 6.95 (d, 1H), 6.63 (1H, 6-OCH$_2$CH*CH*Q), 6.37(1H, 6-OCH$_2$*CH*CHQ) 6.22 (1H, 8a-CO*NH*), 5.00 (1H, H-13), 4.34 (1H, H-5), 4.12 (1H, H-1′), 3.81 (1H, H-2), 3.79 (2H, 6-O*CH*$_2$CHCHQ), 2.39 (6H, 3′-NMe$_2$), 1.35 (3H, 2-Me), 0.89 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 206.3 (s, C-3), 173.2 (s, C-9), 171.4 (s, C-1), 150.0, 148.4, 146.8, 129.6, 129.4, 127.5, 127.1, 126.9, 126.7 (6-OCH$_2$CHCHQ), 133.1 (d, 6-OCH$_2$CH*CH*Q), 128.8 (d, 6-OCH$_2$*CH*CHQ), 101.1 (d, C-1′), 65.3 (t, 6-O*CH*$_2$CHCHQ), 48.7 (d, C-2), 13.9 (q, 2-Me), 11.4 (q, 15-Me). HRMS (ES) calcd for $C_{41}H_{61}N_3O_{10}$ (MH^+) 756.4357, found 756.4347. Anal. Calcd for $C_{41}H_{61}N_3O_{10}$: C, 65.14; H, 8.13; N, 5.56. Found: C, 65.32; H, 8.34; N, 5.30.

The compounds **24a–c** were prepared from 3-oxo-6-*O*-allyl-9a-aza-9a-homoerythromycin A (**19**) as a starting material according to the same procedure as for the synthesis of **23a–c**.

4.2.6.4. 3-Oxo-6-*O*-[3-(1′-naphthyl)-2-propenyl]-9a-aza-9a-homoerythromycin A (24a). FAB-MS *m*/*z* 755 (MH^+, 100%); ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 1H), 7.96 (m, 1H), 7.93 (m, 1H), 7.78 (d, 1H), 7.55 (m, 2H), 7.50 (m, 1H), 6.68 (1H, 9a-CO*NH*), 6.65 (1H, 6-OCH$_2$CH*CH*Ar), 6.31(1H, 6-OCH$_2$*CH*CHAr) 4.68 (1H, H-13), 4.50 (1H, H-5), 4.43 (1H, H-1′), 3.96 (1H, 6-O*CH*$_{2b}$CHCHAr), 3.89 (1H, H-2), 3.73 (1H, 6-O*CH*$_{2a}$CHCHAr), 2.61 (6H, 3′-NMe$_2$), 1.39 (3H, 2-Me), 0.91 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 206.9 (s, C-3), 177.1 (s, C-9), 174.8 (s, C-1), 135.8, 134.3, 133.0, 128.9, 128.3, 126.9, 126.6, 126.2, 124.6, 122.8 (6-OCH$_2$CHCH*Ar*), 130.2 (d, 6-OCH$_2$ CH*CH*Ar), 126.7 (t, 6-OCH$_2$*CH*CHAr), 101.4 (d, C-1′), 62.5 (t, 6-O*CH*$_2$CHCH$_2$), 48.8 (d, C-2), 13.6 (q, 2-Me), 11.7 (q, 15-Me). HRMS (ES) calcd for $C_{42}H_{62}N_2O_{10}$ (MH^+) 755.4404, found 755.4416. Anal. Calcd for $C_{42}H_{62}N_2O_{10}$: C, 66.82; H, 8.28; N, 3.71. Found: C, 67.03; H, 8.40; N, 3.53.

4.2.6.5. 3-Oxo-6-*O*-[3-(3′-quinolyl)-2-propenyl]-9a-aza-9a-homoerythromycin A (24b). FAB-MS *m*/*z* 756 (MH^+, 77%); ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 8.67 (d, 1H), 8.32 (d, 1H), 7.98 (d, 1H), 7.62 (m, 2H), 6.70 (1H, 9a-CO*NH*), 6.50 (1H, 6-OCH$_2$CH*CH*Q), 6.28 (1H, 6-OCH$_2$*CH*CHQ), 4.55 (1H, H-13), 4.45 (1H, H-5), 4.34 (1H, H-1′), 3.99 (1H, 6-O*CH*$_{2b}$CHCHQ), 3.90 (1H, H-2), 3.65 (1H, 6-O*CH*$_{2a}$CHCHQ), 2.51 (6H, 3′-NMe$_2$), 1.41 (3H, 2-Me), 0.88 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 205.3 (s, C-3), 178.5 (s, C-9), 174.2 (s, C-1), 151.5, 149.3, 137.4, 130.1, 129.1, 128.0, 127.6, 127.2, 126.5 (6-OCH$_2$CHCHQ), 131.1 (d, 6-OCH$_2$CH*CH*Q), 127.7 (d, 6-OCH$_2$*CH*CHQ), 101.8 (d, C-1′), 61.9 (t, 6-O*CH*$_2$CHCH$_2$), 47.3 (d, C-2), 13.9 (q, 2-Me), 11.5 (q, 15-Me). HRMS (ES) calcd for $C_{41}H_{61}N_3O_{10}$ (MH^+)

756.4357, found 756.4340. Anal. Calcd for $C_{41}H_{61}N_3O_{10}$: C, 65.14; H, 8.13; N, 5.56. Found: C, 65.28; H, 8.15; N, 5.43.

4.2.6.6. 3-Oxo-6-*O*-[3-(4′-quinolyl)-2-propenyl]-9a-aza-9a-homoerythromycin A (24c). FAB-MS *m*/*z* 756 (MH^+, 77%); ^1H NMR ($CDCl_3$) δ 8.83 (d, 1H), 8.18 (d, 1H), 7.65 (m, 2H), 7.34 (d, 1H), 6.78 (d, 1H), 6.70 (1H, 9a-CO*NH*), 6.58 (1H, 6-OCH$_2$CH*CH*Q), 6.21(1H, 6-OCH$_2$*CH*CHQ), 4.63 (1H, H-13), 4.47 (1H, H-5), 4.21 (1H, H-1′), 4.02 (1H, 6-O*CH*$_{2b}$CHCHQ), 3.96 (1H, H-2), 3.78 (1H, 6-O*CH*$_{2a}$CHCHQ), 2.40 (6H, 3′-NMe$_2$), 1.39 (3H, 2-Me), 0.91 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 205.5 (s, C-3), 179.2 (s, C-9), 173.1 (s, C-1), 150.9, 147.7, 146.5, 129.3, 129.1, 128.3, 127.9, 126.6, 126.1 (6-OCH$_2$CHCH*Q*), 132.1 (d, 6-OCH$_2$CH*CH*Q), 127.6 (d, 6-OCH$_2$*CH*CHQ), 101.7 (d, C-1′), 64.9 (t, 6-O*CH*$_2$CHCHQ), 47.5 (d, C-2), 12.1 (q, 2-Me), 10.7 (q, 15-Me). HRMS (ES) calcd for $C_{41}H_{61}N_3O_{10}$ (MH^+) 756.4357, found 756.4347. Anal. Calcd for $C_{41}H_{61}N_3O_{10}$: C, 65.14; H, 8.13; N, 5.56. Found: C, 65.36; H, 8.17; N, 5.66.

4.2.7. Double Heck reaction on 6,12-di-*O*-allyl-3-oxo-3-*O*-descladinosyl-9a-aza-9a-homoerythromycin A (22). Preparation of 3-oxo-6,12-di-*O*-[3-(3′-quinolyl)-2-propenyl]-9a-aza-9a-homoerythromycin A (25b)

To a solution of 6,12-di-*O*-allyl-3-keto-3-*O*-descladinosyl-9a-aza-9a-homoerythromycin A (200 mg, 0.30 mmoL) in dry DMF (2 mL) were added $Pd(OAc)_2$ (0.4 mol equiv, 0.12 mmoL, 26.9 mg) and P(*o*-tolyl)$_3$ (0.8 mol equiv, 0.24 mmoL, 73.0 mg) and the resulting mixture was stirred for 15 min at room temperature under nitrogen gas. 3-Bromoquinoline (3 mol equiv; 0.90 mmoL, 187.2 mg) and Et_3N (4 mol equiv, 1.20 mmoL, 121.4 mg) were added to the reaction mixture and stirred at 50 °C under nitrogen for 1 h. The temperature was increased to 100 °C and the reaction mixture was stirred for an additional 2 h and 30 min. The mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was separated, and washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl solution (50 mL). The organic layer was dried over K_2CO_3, the solvents were removed under reduced pressure to afford 620 mg of oily residue. The residue was purified by silica gel column chromatography (90:9:0.5; CH_2Cl_2/MeOH/aq NH_3) to afford 143.5 mg (52%) of the product as a colorless solid. FAB-MS *m*/*z* 924 (MH^+, 100%); ^1H NMR ($CDCl_3$) δ 8.80 (s, 2H), 8.30 (m, 2H), 8.10 (m, 2H), 7.98–7.78 (m, 4H), 7.66 (m, 2H), 7.49 (1H, 9a-CO*NH*) 6.56 (1H, 6-OCH$_2$ CH*CH*Q), 6.48 (1H, 12-OCH$_2$CH*CH*Q) 6.32(1H, 6-OCH$_2$*CH*CHQ), 6.20 (1H, 12-OCH$_2$*CH*CHQ), 4.95 (1H, H-13), 4.60 (1H, H-5), 4.45 (1H, H-10), 4.22 (1H, H-1′), 4.00 (2H, 12-O*CH*$_{2b}$), 3.92 (2H, 12-O*CH*$_{2a}$), 3.88 (2H, 6-O*CH*$_{2b}$), 3.75 (2H, 6-O*CH*$_{2a}$), 3.70 (1H, H-2), 3.64 (1H, H-5′), 3.40 (1H, H-2′), 3.31 (1H, H-4), 2.97 (1H, H-3′), 2.65 (6H, 3′-NMe$_2$), 2.60 (1H, H-8), 2.47 (1H, H-7b), 2.20 (1H, H-4′b), 1.92 (1H, H-14b), 1.63 (3H, 10-Me), 1.53 (1H, H-14a), 1.41 (1H, H-4′a), 1.38 (3H, 12-Me), 1.37 (3H, 4-Me), 1.36 (1H, H-7a), 1.35 (3H, 6-Me), 1.30 (3H, 2-Me), 1.28 (3H, 5′-Me), 1.10 (3H, 8-Me), 0.89 (3H, 15-Me). HRMS (ES) calcd for $C_{53}H_{70}N_4O_{10}$ (MH^+) 923.5092, found 923.5065. Anal. Calcd for $C_{53}H_{70}N_4O_{10}$: C, 68.96; H, 7.64; N, 6.07. Found: C, 69.26; H, 7.78; N, 5.83.

4.2.8. Lithium perchlorate-induced regioselective ring opening of epoxides (27a–b)

A mixture of *syn*- and *anti*-epoxides[9] **27a–b** (644 mg, 1.0 mmoL), $LiClO_4$ $3H_2O$ (802.2 mg, 5.0 mmoL, 5.0 mol equiv), and amine **a–m** (5.0 mmoL, 5.0 mol equiv) in 2-propanol (2.5 mL) was heated at reflux during 24 h. Upon completion of the reaction as indicated by TLC or LC/MS, the solution was cooled to room temperature, and CH_2Cl_2 (25 mL) was added. The organic layer was washed with water (2 × 25 mL), dried, and concentrated in vacuo. The residual solid was purified by chromatography on silica gel using CH_2Cl_2/methanol/aq NH_3 (90:9:1.5) as eluent to give a mixture of diastereoisomeric β-amino alcohols (**28aa–am** and **28ba–bm**; 50–80% isolated yield) in ratio 1:1 according to LC/MS analysis.

4.2.8.1. 6-{2″-(*syn*,*anti*)-Hydroxy-3″-[4-(isoquinoline-7-sulfonyl)-2-methyl-piperazin-1-yl]-propoxy}-3-oxo-8a-aza-8a-homoerythromycin A (28af–bf). FAB-MS *m*/*z* 936 (MH^+, 78%); ^1H NMR ($CDCl_3$) δ 9.34 (s, 1H, H-4Ar), 8.67 (d, 1H, H-6Ar), 8.55 (d, 1H, H-5Ar), 8.36 (dd, 1H, H-1Ar), 8.21 (dd, 1H, H-3Ar), 7.71 (ddd, 1H, H-2Ar), 5.49 (d, 1H, 8a*NH*), 4.89 (dd, 1H, H-13), 4.40 (d, 1H, H-1′), 4.27–4.16 (m, 1H, H-8), 3.85–3.71 (m, 2H, H-5, H-2), 3.67 (br s, 1H, H-2″), 3.59 (d, 1H, H-1″b), 3.54–3.43 (m, 1H, H-5′), 3.38 (s, 1H, H-11), 3.24 (t, 1H, H-1″a), 3.22–3.15 (m, 1H, H-2′), 3.05 (t, 1H, H-4), 2.95–2.86 (m, 4H, H-5″, H-6″), 2.50 (t, 1H, H-3″b), 2.48–2.40 (m, 1H, H-3′), 2.38 (s, 1H, 12-OH), 2.35 (d, 1H, H-2″b), 2.30 (s, 6H, 3′-NMe$_2$), 2.28 (dd, 1H, H-10), 2.25 (dd, 1H, H-3″a), 2.13 (dd, 1H, H-4″), 2.00 (s, 1H, 11-OH), 1.93 (ddq, 1H, H-14b), 1.72 (dd, 1H, H-7b), 1.59 (d, 1H, H-7a), 1.51 (dd, 1H, H-2″a), 1.44 (ddq, 1H, H-14a), 1.35 (s, 3H, 6-Me), 1.32 (d, 3H, 2-Me), 1.29 (d, 3H, 4-Me), 1.21 (d, 3H, 5′-Me), 1.14 (d, 3H, 10-Me), 1.13 (s, 3H, 12-Me), 1.11 (d, 3H, 8-Me), 0.92 (d, 3H, 4″-Me), 0.85 (t, 3H, 15-Me). HRMS (ES) calcd for $C_{46}H_{73}N_5O_{13}S$ (MH^+) 936.4926, found 936.4896. Anal. Calcd for $C_{46}H_{73}N_5O_{13}S$: C, 59.02; H, 7.86; N, 7.48. Found: C, 59.13; H, 7.91; N, 7.21.

4.2.8.2. 6-[2″-(*syn*,*anti* -Hydroxy-3″-isobutylamino-propoxy]-3-oxo-8a-aza-8a-homoerythromycin A (28ag–bg). FAB-MS *m*/*z* 718 (MH^+, 67%); ^1H NMR ($CDCl_3$) δ 5.59 (d, 1H, 8a*NH*), 5.03 (dd, 1H, H-13), 4.50 (d, 1H, H-1′), 4.34–4.24 (m, 1H, H-8), 3.85 (d, 1H, H-5), 3.80 (m, 1H, H-2), 3.72–3.65 (m, 2H, H-2″, H-1″b), 3.64–3.57 (m, 1H, H-5′), 3.43–3.38 (m, 1H, H-1″a), 3.37 (s, 1H, H-11), 3.17 (dd, 1H, H-2′), 2.68 (dd, 1H, H-3″a), 2.59–2.50 (m, 2H, H-4″b, H-3″a), 2.45 (m, 1H, H-3′), 2.42–2.37 (m, 1H, H-4″a), 2.35 (s, 6H, 3′-NMe$_2$), 2.31 (dd, 1H, H-10), 1.99–1.91 (m, 2H, H-14b, H-4′b), 1.87 (dt, 1H, H-4), 1.80–1.70 (m, 2H, H-7b, H-5″), 1.64 (d, 1H, H-7a), 1.48 (ddq, 1H, H-14a), 1.39 (s, 3H, 6-Me), 1.34 (d, 1H, H-4′a), 1.27 (d, 3H, 5′-Me), 1.21 (d, 3H, 2-Me), 1.18 (d, 3H, 10-Me), 1.16 (s, 3H, 12-Me), 1.14 (d, 3H, 4-Me), 1.13 (d, 3H, 8-Me), 0.91 (d, 6H, 6″-Me$_2$), 0.86 (t, 3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 205.0 (s, C-3), 175.3 (s, C-9), 170.2 (s, C-1), 102.8 (d, C-1′), 79.5 (s, C-6), 79.1 (d, C-5), 77.4 (d, C-13), 74.4 (s, C-12), 71.4 (d, C-11), 70.5 (d, C-2′), 67.5 (d, C-2″), 67.3 (d, C-5′), 66.9 (t, C-1″), 65.5 (d, C-3′), 50.7 (t, C-3″), 50.0 (t, C-4″), 49.8 (d, C-2), 46.5 (d, C-4), 43.3 (t, C-7), 42.9 (d, C-10), 40.8 (d, C-8), 40.4 (q, 3′-NMe$_2$), 35.0 (t, C-2″), 30.0 (t, C-4′), 26.9 (d, C-5″), 24.3 (q, 6-Me), 24.2 (q, 8-Me), 21.6 (q, 5′-Me), 21.1 (t, C-14), 20.6 (q, 6″-Me, 1C), 20.2 (q, 6″-Me, 1C), 16.5 (q, 12-Me), 14.8 (q, 4-Me) 13.9 (q, 2-Me), 10.9 (q, 15-Me), 9.3 (q, 10-Me). HRMS (ES) calcd for $C_{36}H_{67}N_3O_{11}$ (MH^+) 718.4776, found 718.4762. Anal. Calcd for $C_{36}H_{67}N_3O_{11}$: C, 60.23; H, 9.41; N, 5.85. Found: C, 60.58; H, 9.43; N, 5.61.

A mixture of **28ai** and **28bi** was separated by reversed-phase HPLC to afford **28ai** and its epimeric β-hydroxy alcohol **28bi** as separate solutions in MeOH-H_2O. Solvents were removed in vacuo to give pure **28ai** (10.3 mg) and **28bi** (4.0 mg) as colorless solids.

4.2.8.3. 1-Cyclopropyl-7-[(3-oxo-8a-aza-8a-homoerythromycin-6-yloxy)-(2″-*syn*-hydroxypropyl)piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (28ai). FAB-MS *m*/*z* 976 (MH^+, 84%); ^1H NMR ($CDCl_3$) δ 8.63 (s, 1H, H-Ar), 7.52 (d, 1H, *J* = 7.3 Hz, H-Ar), 7.46 (d, 1H, *J* = 13.0 Hz, H-Ar), 6.17 (br s, 1H, 8a*NH*), 4.99 (dd, 1H, H-13), 4.39 (d, 1H, H-1′), 4.20–4.11 (m, 1H, H-8), 3.83 (m, 1H, H-2), 3.78 (d, 1H, H-5), 3.72 (d, 1H, H-1″b), 3.68–3.65 (m, 1H, H-2″), 3.60 (d, 4H, *J* = 2.0 Hz, H-5″), 3.55 (d, 4H, *J* = 2.0 Hz, H-4″), 3.50–3.46 (m, 1H, H-5′), 3.44 (s, 1H, H-11), 3.40 (dd, 1H, H-1″a), 3.18 (dd, 1H, H-2′), 3.07 (m, 1H, H-4), 3.05–2.99 (m, 1H, H-3″b), 2.54–2.44 (m, 1H, H-3′), 2.32 (s, 6H, 3′-NMe$_2$),

2.30–2.25 (m, 1H, H-10), 2.20 (d, 1H, H-3″a), 1.98–1.87 (m, 2H, H-14b, H-7b), 1.77–1.70 (m, 1H, H-4′b), 1.68–1.63 (m, 1H, H-7a), 1.51–1.47 (m, 1H, H-14a), 1.47 (d, 2H, *J* = 6.5 Hz), 1.42 (s, 3H, 6-Me), 1.35 (d, 3H, 2-Me), 1.31 (d, 3H, 4-Me), 1.24 (d, 3H, 5′-Me), 1.23–1.22 (m, 1H, H-4′a), 1.20 (d, 2H), 1.18 (d, 3H, 10-Me), 1.16 (s, 3H, 12-Me), 1.14 (d, 3H, 8-Me), 0.84 (t, 3H, 15-Me); HRMS (ES) calcd for $C_{49}H_{74}FN_5O_{14}$ (MH^+) 976.5216, found 976.5212. Anal. Calcd for $C_{49}H_{74}FN_5O_{14}$: C, 60.29; H, 7.64; N, 7.17. Found: C, 60.38; H, 7.70; N, 7.00.

4.2.8.4. 1-Cyclopropyl-7-[(3-oxo-8a-aza-8a-homoerythromycin-6-yloxy)-(2″-*anti*-hydroxypropyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (28bi). FAB-MS *m*/*z* 976 (MH^+, 71%); ^1H NMR ($CDCl_3$) δ 8.65 (s, 1H, H-Ar), 7.55 (d, 1H, *J* = 7.3 Hz, H-Ar), 7.48 (d, 1H, *J* = 13.0 Hz, H-Ar), 6.74 (d, 1H, 8a*NH*), 4.63 (dd, 1H, H-13), 4.40 (d, 1H, H-1′), 4.27–4.16 (m, 1H, H-8), 3.95–3.90 (m, 2H, H-5, H-2), 3.64 (br s, 1H, H-2″), 3.66 (d, 4H, *J* = 2.0 Hz, H-5″), 3.56 (d, 4H, *J* = 2.0 Hz, H-4″), 3.43 (d, 1H, H-1″b), 3.39–3.30 (m, 1H, H-5′), 3.28 (s, 1H, H-11), 3.24 (t, 1H, H-1″a), 3.22–3.15 (m, 1H, H-2′), 3.10 (m, 1H, H-4), 2.50 (t, 1H, H-3″b), 2.48–2.40 (m, 1H, H-3′), 2.37 (s, 1H, 12-OH), 2.30 (s, 6H, 3′-NMe_2), 2.28 (dd, 1H, H-10), 1.93 (ddq, 1H, H-14b), 1.72 (dd, 1H, H-7b), 1.59 (d, 1H, H-7a), 1.48 (d, 2H, *J* = 6.5 Hz), 1.44 (m, 1H, H-14a), 1.35 (s, 3H, 6-Me), 1.32 (d, 3H, 2-Me), 1.31 (d, 3H, 4-Me), 1.24 (d, 2H), 1.21 (d, 3H, 5′-Me), 1.14 (d, 3H, 10-Me), 1.13 (s, 3H, 12-Me), 1.11 (d, 3H, 8-Me), 0.85 (t, 3H, 15-Me). HRMS (ES) calcd for $C_{49}H_{74}FN_5O_{14}$ (MH^+) 976.5216, found 976.5210. Anal. Calcd for $C_{49}H_{74}FN_5O_{14}$: C, 60.29; H, 7.64; N, 7.17. Found: C, 60.35; H, 7.67; N, 7.05.

4.2.8.5. 1-Cyclopropyl-7-[(3-oxo-8a-aza-8a-homoerythromycin-6-yloxy)-(2″-*syn*,*anti*-hydroxypropylamino)ethylamino)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (28al–bl). FAB-MS *m*/*z* 950 (MH^+, 55%); ^1H NMR ($CDCl_3$) δ 8.66 (s, 1H, H-Ar), 7.59 (d, 1H, *J* = 7.3 Hz, H-Ar), 7.50 (d, 1H, *J* = 13.0 Hz, H-Ar), 6.25 (1H, 8a*NH*), 5.02 (1H, H-13), 4.45 (1H, H-1′), 4.25 (1H, H-8), 3.91 (1H, H-2), 3.85 (1H, H-5), 3.76 (1H, H-1″b), 3.65 (1H, H-2″), 3.50 (1H, H-5′), 3.45 (1H, H-11), 3.41 (1H, H-1″a), 3.15 (1H, H-2′), 3.05 (1H, H-4), 2.83 (1H, H-3″b), 2.78 (2H, H-4″), 2.52–2.41 (1H, H-3′), 2.37 (6H, 3′-NMe_2), 2.30 (1H, H-10), 2.58 (1H, H-3″a), 1.98–1.88 (2H, H-14b, H-7b), 1.75–1.69 (m, 1H, H-4′b), 1.65 (1H, H-7a), 1.48 (1H, H-14a), 1.45 (d, 2H, *J* = 6.4 Hz), 1.40 (3H, 6-Me), 1.32 (3H, 2-Me), 1.28 (3H, 4-Me), 1.25 (d, 2H), 1.22 (3H, 5′-Me), 1.20 (1H, H-4′a), 1.16 (3H, 10-Me), 1.14 (3H, 12-Me), 1.10 (3H, 8-Me), 0.90 (3H, 15-Me). HRMS (ES) calcd for $C_{47}H_{72}FN_5O_{14}$ (MH^+) 950.5060, found 950.5084. Anal. Calcd for $C_{47}H_{72}FN_5O_{14}$: C, 59.42; H, 7.64; N, 7.37. Found: C, 59.70; H, 7.73; N, 7.30.

According to the above general procedure for epoxide ring opening following derivatives were also prepared: **28ac–bc**,[9] **28ah–bh**, **28aj–bj**, **28ak–bk**, and **28am–bm**.

Compounds **28ah–bh**: ^1H NMR ($CDCl_3$) δ 8.70 (s, 1H), 8.03 (s, 1H), 7.59 (s, 1H), 5.85 (br s, 1H), 4.94 (m, 1H), 4.43 (d, 1H), 4.24–3.75 (m, 4H), 3.70–3.05 (m, 8H), 2.90 (m, 2H), 2.85–2.60 (m, 2H), 2.50 (m, 1H), 2.40 (br s, 3H), 2.30 (m, 6H), 2.21 (s, 3H), 2.00 (m, 1H), 1.97 (m, 2H), 1.67 (m, 2H), 1.46 (s, 3H), 1.36 (d, 3H), 1.30 (d, 3H), 1.27 (d, 3H), 1.20 (d, 3H), 0.81 (t, 3H). HRMS (ES) calcd for $C_{49}H_{74}ClN_5O_{14}$ (MH^+) 992.4921, found 992.4937. Anal. Calcd for $C_{49}H_{74}ClN_5O_{14}$: C, 59.29; H, 7.51; N, 7.06. Found: C, 59.60; H, 7.88; N, 6.82.

Compounds **28aj–bj**: ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.93 (d, 1H), 7.42 (d, 1H), 7.20 (dd, 1H), 6.20 (d, 1H), 5.05 (dd, 1H), 4.48 (d, 1H), 4.32–3.78 (m, 3H), 3.72–3.40 (m, 3H), 3.42 (s, 1H), 3.35–3.25 (m, 5H), 3.20 (d, 1H), 3.05–2.82 (m, 2H), 2.56–2.46 (m, 1H), 2.31 (s, 6H), 2.25 (m, 1H), 2.10 (d, 1H), 2.05–1.85 (m, 2H), 1.80–1.61 (m, 2H), 1.49 (m, 1H), 1.43 (s, 3H), 1.35 (d, 3H), 1.30 (d, 3H), 1.22 (d, 3H), 1.20 (m, 1H), 1.18 (d, 3H), 1.15 (s, 3H), 1.12 (d, 3H), 0.85 (t, 3H). HRMS (ES) calcd for $C_{49}H_{75}N_5O_{14}$ (MH^+) 958.5311, found 958.5339. Anal. Calcd for $C_{49}H_{75}N_5O_{14}$: C, 61.42; H, 7.89; N, 7.31. Found: C, 61.59; H, 7.93; N, 6.98.

Compounds **28ak–bk**: ^1H NMR ($CDCl_3$) δ 8.73 (s, 1H), 8.05 (s, 1H), 7.53 (s, 1H), 6.31 (br s, 1H), 5.97 (d, 1H), 5.11 (dd, 1H), 4.46 (m, 1H), 4.20 (m, 1H), 4.01 (m, 1H), 3.86 (m, 2H), 3.71 (m, 1H), 3.63 (m, 1H), 3.56 (m, 1H), 3.51 (s, 1H), 3.47 (m, 1H), 3.40–3.26 (m, 3H), 3.20–3.09 (m, 4H), 3.05 (m, 1H), 2.46 (m, 1H), 2.28 (s, 6H), 2.24 (m, 1H), 1.97–1.91 (m, 2H), 1.87–1.72 (m, 2H), 1.40 (d, 3H), 1.31 (s, 3H), 1.29 (d, 3H), 1.26 (d, 3H), 1.20 (d, 3H), 1.18 (d, 3H), 1.16 (s, 3H), 0.86 (t, 3H). HRMS (ES) calcd for $C_{47}H_{72}ClN_5O_{14}$ (MH^+) 966.4764, found 966.4769. Anal. Calcd for $C_{47}H_{72}ClN_5O_{14}$: C, 58.40; H, 7.51; N, 7.25. Found: C, 58.75; H, 7.59; N, 6.87.

Compounds **28am–bm**: ^1H NMR ($CDCl_3$) δ 8.64 (s, 1H), 7.50 (d, 1H), 7.44 (d, 1H), 6.19 (br s, 1H), 4.97 (dd, 1H), 4.36 (d, 1H), 4.20–4.10 (m, 1H), 3.82 (m, 1H), 3.76 (d, 1H), 3.71 (d, 1H), 3.67–3.62 (s+m, 4H), 3.59 (d, 4H), 3.54 (d, 4H), 3.50–3.45 (m, 1H), 3.42 (s, 1H), 3.38 (dd, 1H), 3.20 (dd, 1H), 3.08 (m, 1H), 3.04–2.97 (m, 1H), 2.56–2.41 (m, 1H), 2.30 (s, 6H), 2.28–2.23 (m, 1H), 2.19 (d, 1H), 2.00–1.86 (m, 2H), 1.79–1.69 (m, 1H), 1.65–1.60 (m, 1H), 1.50–1.46 (m, 1H), 1.43 (d, 2H), 1.40 (s, 3H), 1.34 (d, 3H), 1.30 (d, 3H), 1.25 (d, 3H), 1.22 (m, 1H), 1.20 (d, 2H), 1.18 (d, 3H), 1.16 (s, 3H), 1.14 (d, 3H), 0.84 (t, 3H). HRMS (ES) calcd for $C_{50}H_{76}FN_5O_{14}$ (MH^+) 990.5373, found 990.5389. Anal. Calcd for $C_{50}H_{76}FN_5O_{14}$: C, 60.65; H, 7.74; N, 7.07. Found: C, 60.74; H, 7.84; N, 6.90.

4.2.9. 9,2′-Di-*O*-acetyl-3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime (29)

To a solution of 3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime[9] (**7**) (1.50 g, 2.38 mmoL) in methylene chloride was added acetic anhydride (2.2 mol equiv, 4.62 mmoL, 471.7 mg). Triethylamine (2.2 mol equiv, 4.62 mmoL, 467.5 mg) was added over 5 min, and the thick solution was stirred for 12 h. After 2 h stirring at room temperature the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL), and the mixture was stirred for an additional 30 min. The layers were separated, and the aqueous layer was extracted twice with methylene chloride (2 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over potassium carbonate, filtered and concentrated in vacuo. The oily residue was purified by silica gel column chromatography (eluent: hexane/acetone/aq NH_3, 50:50:0.5) to give 1.53 g (90%) of 2′,9-di-*O*-acetyl-(*E*)-oxime (**29**) as a colorless solid: FAB-MS *m*/*z* 715 (MH^+, 77%); ^1H NMR ($CDCl_3$) δ 6.06 (m, 1H), 5.42 (dd, 1H), 5.28 (dd, 1H), 4.04 (dd, 2H), 3.83 (m, 1H), 2.37 (br s, 6H), 2.28 (s, 3H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 176.3, 171.1, 170.2, 168.3, 134.1, 117.6, 70.9, 67.9, 42.0, 21.0, 19.4.

4.2.10. 9,2′-Di-*O*-acetyl-3-oxo-6-*O*-allylerythromycin A 9(*E*)-oxime (30)

To a solution of 2′,9-di-*O*-acetyl-3-*O*-descladinosyl-6-*O*-allylerythromycin A 9(*E*)-oxime (**29**) (1.20 g, 1.68 mmoL) in methylene chloride (5.0 mL) was added $NaHCO_3$ (10 mol equiv, 16.8 mmoL, 1.41 g) and pyridine (5 mol equiv, 8.4 mmoL, 664.4 mg), and the resulting suspension was chilled to 0 °C and stirred for an additional 10 min. Dess–Martin periodinane (2 mol equiv, 3.36 mmoL, 1.43 g) was added in small portions over 10 min, and the reaction was stirred for an additional 2 h. After the reaction was complete as indicated by TLC analysis (hexane/acetone/aq NH_3, 50:50:0.5) saturated aqueous $Na_2S_2O_3$ (50 mL) was added to the reaction mixture, and the aqueous phase was extracted with methylene chloride (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over K_2CO_3 and concentrated in vacuo to provide a crude residue which was purified by flash chromatography (hexane/acetone/aq NH_3, 50:50:0.5) to afford 933.4 mg (78%) of ketolide **30** as a colorless solid. FAB-MS *m*/*z* 713 (MH^+, 65%); ^1H NMR ($CDCl_3$) δ 6.04 (m, 1H), 5.45 (dd, 1H), 5.26 (dd,

1H), 4.06 (dd, 2H), 3.80 (m, 1H), 2.38 (br s, 6H), 2.28 (s, 3H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 211.3, 172.0, 171.5, 170.8, 169.2, 133.5, 118.1, 68.3, 42.0, 21.2, 20.3.

4.2.11. 9,2′-Di-*O*-acetyl-3-oxo-6-*O*-[3-(3′-quinolyl)-2-propenyl]erythromycin A 9(*E*)-oxime (31)

To a solution of ketolide (**30**) (1.0 g, 1.40 mmoL), palladium(II) acetate (67 mg, 0.30 mmoL), and tri(*o*-tolyl)phosphine (181 mg, 0.60 mmoL) in dry acetonitrile (7 mL) were added 3-bromoquinoline (2 mol equiv, 2.8 mmoL, 582.5 mg), and triethylamine (4 mol equiv, 5.6 mmoL, 566.7 mg), and the mixture was stirred under argon for 30 min. The reaction mixture was warmed to 60 °C for 2 h and stirred at 90 °C for 20 h. The reaction mixture was taken up in ethyl acetate, washed with saturated aqueous sodium bicarbonate, and with brine, and dried over sodium sulfate. The solvent was removed in vacuo to give the crude product (964.3 mg, 82%), which was used in the next step without further purification. FAB-MS *m*/*z* 840 (MH^+, 56%). ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 8.38 (s, 1H), 8.06 (m, 1H), 7.98 (m, 1H), 7.78 (m, 1H), 7.60 (m, 1H), 6.65 (d, 1H), 6.25 (m, 1H), 4.10 (dd, 2H), 3.79 (m, 1H), 2.40 (br s, 6H), 2.26 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 211.5, 172.4, 171.1, 170.2, 169.5, 149.3, 147.9, 135.9, 132.5, 129.7, 129.1, 128.5, 128.4, 128.3, 127.6, 69.6, 42.0, 21.0, 19.4.

4.2.12. 9-*O*-Acetyl-3-oxo-6-*O*-[3-(3′-quinolyl)-2-propenyl]erythromycin A 9(*E*)-oxime (32)

Compound **31** (840 mg, 1.0 mmoL) was dissolved in methanol (5 mL) and the solution was heated under reflux for 12 h, after which time the end of the reaction was established (TLC). The crude product obtained after evaporation of solvent was purified by flash chromatography (silica gel, hexane/acetone/aq NH_3) to give the title compound **32** (558.6 mg, 70%) as a colorless foam. FAB-MS *m*/*z* 798 (MH^+, 68%). ^{1}H NMR ($CDCl_3$) δ 8.87 (s, 1H), 8.35 (s, 1H), 8.03 (m, 1H), 7.95 (m, 1H), 7.71 (m, 1H), 7.62 (m, 1H), 6.66 (d, 1H), 6.27 (m, 1H), 4.07 (dd, 2H), 3.75 (m, 1H), 2.41 (br s, 6H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 211.4, 172.0, 171.4, 169.7, 169.2, 149.3, 147.9, 136.0, 132.3, 129.8, 129.1, 128.7, 128.1, 128.5, 127.3, 69.9, 42.0, 19.9.

4.2.13. 3-Oxo-6-*O*-[3-(3′-quinolyl)-2-propenyl]erythromycin A 9(*E*)-oxime (33)

To a solution of protected oxime **32** (200 mg, 0.25 mmoL) in methanol (10 mL) was added triethylamine (506.0 mg, 5 mmoL), and the reaction mixture was kept under reflux for 5 h. Removal of the solvent under reduced pressure afforded a colorless solid, which was purified by flash chromatography using methylene chloride/methanol/aq NH_3 (90:9:0.5) as eluent to give **33** (141.7 mg, 75%) as a colorless solid. FAB-MS *m*/*z* 756 (MH^+, 93%). ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 8.39 (s, 1H), 8.10 (m, 1H), 7.99 (m, 1H), 7.75 (m, 1H), 7.42 (m, 1H), 6.46 (d, 1H), 6.38 (m, 1H), 4.01 (dd, 2H), 3.78 (m, 1H), 2.40 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 211.3, 172.0, 171.2, 149.5, 147.7, 135.9, 132.5, 129.7, 129.1, 128.4, 128.3, 127.6, 127.2, 69.6, 42.3. HRMS (ES) calcd for $C_{41}H_{61}N_3O_{10}$ (MH^+) 756.4357, found 756.4344. Anal. Calcd for $C_{41}H_{61}N_3O_{10}$: C, 65.14; H, 8.13; N, 5.56. Found: C, 65.23; H, 8.41; N, 5.45.

4.2.14. 3-Oxo-6-*O*-[3-(3′-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A-11,12-cyclocarbonate (34)

A suspension of ketolide **23b** (200 mg, 0.26 mmol), ethylene carbonate (91.6 mg, 1.04 mmoL), and K_2CO_3 (287.5 mg, 2.08 mmoL) in toluene (5 mL) was refluxed with vigorous stirring. After 18 h more ethylene carbonate (287.5 mg, 2.08 mmoL) was added, and the reaction mixture refluxed for an additional 18 h. The reaction mixture was then diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (2 × 50 ml), and brine (2 × 50 mL), dried (K_2CO_3), and concentrated to afford the crude product as a colorless solid (200 mg). Chromatographic purification (silica gel, acetone/hexane 1:1) afforded the product as a colorless foam (155.2 mg, 75% yield). FAB-MS *m*/*z* 782 (MH^+, 92%); ^{1}H NMR ($CDCl_3$) δ 9.01 (d, 1H, *J* = 1.8 Hz), 8.20 (d, 1H, *J* = 1.8 Hz), 8.08 (d, 1H, *J* = 8.3 Hz), 7.86 (d, 1H, *J* = 8.3 Hz), 7.62 (m, 1H), 7.53 (m, 1H) 6.46 (1H, 6-OCH_2CH*CH*Q), 6.38(1H, 6-OCH_2*CH*CHQ) 6.17 (1H, 8a-CO*NH*), 5.12 (1H, H-13), 4.30 (1H, H-5), 4.27 (1H, H-1′), 3.96 (1H, H-8), 3.80 (1H, H-2), 3.73 (2H, 6-O*CH*$_2$CHCHQ), 3.58 (1H, H-5′), 3.72 (1H, H-11), 3.25 (1H, H-2′), 3.10 (1H, H-4), 2.62 (1H, H-3′), 2.69 (1H, H-10), 2.36 (6H, 3′-NMe_2), 1.98–1.93 (2H, H-14b, H-7b), 1.75 (1H, H-4′a), 1.61 (1H, H-7a), 1.57 (1H, H-14a), 1.36 (3H, 2-Me), 1.34 (3H, 4-Me), 1.25 (3H, 6-Me), 1.26 (3H, 5′-Me), 1.20 (3H, 8-Me), 1.16 (3H, 12-Me), 0.87 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 206.2 (s, C-3), 174.4 (s, C-9), 170.5 (s, C-1), 154.2 (s, CO carbonate), 149.6, 147.5, 132.5, 129.8, 129.1, 129.0, 128.0, 126.7 (6-OCH_2CH*CH*Q), 129.8 (d, 6-OCH_2CH*CH*Q), 128.4 (d, 6-OCH_2*CH*CHQ), 102.4 (d, C-1′), 79.6 (s, C-6) 76.5 (d, C-5), 78.5 (d, C-13), 73.8 (s, C-12), 72.5 (d, C-11), 69.9 (d, C-2′), 69.4 (d, C-5′), 65.0 (d, C-3′), 64.2 (t, 6-O*CH*$_2$CHCHQ), 49.7 (d, C-2), 46.5 (d, C-4), 43.9 (d, C-8), 44.1 (d, C-10), 41.5 (t, C-7), 40.0 (q, 3′-NMe_2), 28.4 (t, C-4′), 22.5 (q, 8-Me), 22.7 (q, 6-Me), 21.7 (t, C-14), 21.0 (q, 5′-Me), 17.0 (q, 12-Me), 14.5 (q, 4-Me), 13.9 (q, 2-Me), 10.9 (q, 15-Me), 8.5 (q, 10-Me). HRMS (ES) calcd for $C_{42}H_{59}N_3O_{11}$ (MH^+) 782.4150, found 782.4168. Anal. Calcd for $C_{42}H_{59}N_3O_{11}$: C, 64.51; H, 7.61; N, 5.37. Found: C, 64.80; H, 7.85; N, 5.40.

4.2.15. Catalytic hydrogenation of 3-oxo-6-*O*-[3-(3′-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A (23b). Preparation of 3-oxo-6-*O*-[3-(3′-tetrahydroquinolyl)-2-propyl]-8a-aza-8a-homoerythromycin A (35)

To a solution of **23b** (230 mg, 0.30 mmoL) in MeOH (10 mL) under nitrogen atmosphere was added 10% Pd-C catalyst (50 mg). The mixture was stirred under hydrogen atmosphere for 17 h. The catalyst was removed by filtration and the filtrate was concentrated. Column chromatography (silica gel, 95:5:0.5 CH_2Cl_2/MeOH/aq ammonia) of the crude product provided **35** (143.7 mg, 62%) as a colorless solid. FAB-MS *m*/*z* 762 (MH^+, 72%); ^{1}H NMR ($CDCl_3$) δ 7.07 (m, 1H), 7.05 (m, 1H), 6.72 (m, 1H), 6.70 (m, 1H), 5.28 (br s, NH), 6.15 (1H, 8a-CO*NH*), 5.03 (1H, H-13), 4.25 (1H, H-5), 4.22 (1H, H-1′), 3.82 (1H, H-8), 3.70 (1H, H-2), 3.62 (1H, H-5′), 3.51 (1H, H-11), 3.32 (m, 2H), 3.20 (1H, H-2′), 3.12 (m, 2H), 3.01 (1H, H-4), 2.60 (1H, H-3′), 2.52 (m, 2H), 2.41 (1H, H-10), 2.31 (6H, 3′-NMe_2), 2.10 (m, 1H), 2.00–1.90 (2H, H-14b, H-7b), 1.72 (1H, H-4′a), 1.59 (1H, H-7a), 1.50 (1H, H-14a), 1.43 (m, 2H), 1.35 (3H, 2-Me), 1.32 (3H, 4-Me), 1.25 (3H, 6-Me), 1.23 (m, 2H), 1.21 (3H, 5′-Me), 1.18 (3H, 8-Me), 1.16 (3H, 12-Me), 0.90 (3H, 15-Me). HRMS (ES) calcd for $C_{41}H_{67}N_3O_{10}$ (MH^+) 762.4826, found 762.4837. Anal. Calcd for $C_{41}H_{67}N_3O_{10}$: C, 64.63; H, 8.86; N, 5.51. Found: C, 64.75; H, 8.89; N, 5.36.

4.2.16. General procedure for the Heck reaction

4.2.16.1. Preparation of 6-*O*-[3-(3′-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A (37b). A mixture of 6-*O*-allyl 8a-lactam **36** (200.0 mg, 0.25 mmoL), 3-bromoquinoline (0.102 mL, 0.76 mmoL), $Pd(OAc)_2$ (17.0 mg, 0.076 mmoL), P(*o*-tolyl)$_3$ (46.0 mg, 0.152 mmoL), and Et_3N (0.106 mL, 0.76 mmoL) in acetonitrile (10 mL) was flushed with nitrogen and sealed in a pressure tube. The reaction mixture was heated to 60 °C for 1 h and then to 90 °C for 48 h. The reaction mixture was taken up in ethyl acetate and washed with 5% aqueous Na_2CO_3 and brine. The organic phase was concentrated under reduced pressure and purified by column chromatography, eluted with 10% MeOH in methylene chloride containing 0.5% aqueous NH_3, to give the title compound (190.4 mg, 82%). ESI-MS *m*/*z* 916 (MH^+, 99%); ^{1}H NMR ($CDCl_3$) δ 9.03 (d, 1H, *J* = 1.8 Hz), 8.18 (d, 1H, *J* = 1.8 Hz), 8.06 (d, 1H,

J = 8.3 Hz), 7.84 (d, 1H, *J* = 8.3 Hz), 7.65 (m, 1H), 7.52 (m, 1H), 6.68 (m, 1H, 6-OCH$_2$*CH*CHQ), 6.45 (d, 1H, 8a*NH*), 6.32 (d, 1H, *J* = 14.0 Hz, 6-OCH$_2$CH*CH*Q), 3.97 (dd, 1H, 6-O*CH*$_2$CHCHQ). ^{13}C NMR ($CDCl_3$) δ 149.6, 147.5, 132.5, 129.8, 129.1, 129.0, 128.0, 126.7 (6-OCH$_2$CHCHQ), 129.8 (d, 6-OCH$_2$CH*CH*Q), 128.4 (d, 6-OCH$_2$*CH*CHQ), 79.6 (s, C-6), 64.2 (t, 6-O*CH*$_2$CHCHQ). HRMS (ES) calcd for $C_{49}H_{77}N_3O_{13}$ (MH^+) 916.5456, found 916.5430. Anal. Calcd for $C_{49}H_{77}N_3O_{13}$: C, 64.24; H, 8.47; N, 4.59. Found: C, 64.35; H, 8.53; N, 4.46.

4.2.16.2. Preparation of 6-*O*-[3-(1′-naphthyl)-2-propenyl]-8a-aza-8a-homoerythromycin A (37a). According to the same general procedure for the synthesis of **37b**, 250 mg of **36** (0.32 mmoL) afforded **37a** (159.5 mg, 55%). ESI-MS *m*/*z* 915 (MH^+, 99%); ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1H), 7.99 (d, 1H), 7.96 (d, 1H), 7.81 (d, 1H), 7.64 (m, 2H), 7.58 (m, 1H), 6.15 (1H, 8a-CO*NH*), 4.94 (1H, H-13), 4.90 (1H, H-1″), 4.32 (1H, H-1′), 4.32 (1H, H-8), 4.06 (1H, H-5″), 3.97 (1H, H-3), 3.77 (1H, H-5), 3.44 (1H, H-5′), 3.36 (1H, H-11), 3.17 (1H, H-2′), 3.07 (1H, H-4″), 2.98 (3H, 3″-OMe), 2.77 (1H, H-2), 2.41 (1H, H-3′), 2.25 (3H, 3′-NMe$_2$), 1.45 (3H, 6-Me), 1.32 (3H, 5″-Me), 1.22 (3H, 3″-Me), 1.20 (3H, 5′-Me), 1.18 (3H, 2-Me), 1.16 (3H, 10-Me), 1.14 (3H, 12-Me), 1.13 (6H, 8-Me, 4-Me), 0.85 (3H, 15-Me). ^{13}C NMR ($CDCl_3$) δ 177.0 (s, C-1), 174.8 (s, C-9), 136.8, 134.5, 131.4, 129.5, 128.2, 128.1, 126.7, 126.5, 126.0, 125.3, (Aryl C) 124.2 (6-OCH$_2$CH*CH*Ar), 121.7 (6-OCH$_2$*CH*CHAr), 103.2 (d, C-1′), 97.1 (d, C-1″), 78.8 (d, C-5), 78.7 (s, C-6), 78.2 (d, C-3), 77.9 (d, C-4″), 77.0 (d, C-13), 73.9 (s, C-12), 73.2 (s, C-3″), 71.3 (d, C-11), 70.5 (d, C-2′), 68.9 (d, C-5′), 65.7 (d, C-5″, C-3′), 63.5 (t, 6-O*CH*$_2$CHCHAr) 49.8 (q, 3″-OMe), 45.1 (d, C-2), 42.3 (t, C-7), 42.5 (d, C-4), 42.0 (d, C-10), 40.8 (d, C-8), 40.0 (q, 3′-NMe$_2$), 35.7 (t, C-2″), 27.7 (t, C-4′), 24.8 (q, 6-Me), 22.5 (q, 8-Me), 21.4 (q, 5′-Me), 21.3 (q, 3″-Me), 21.0 (t, C-14), 18.9 (q, 5″-Me), 16.3 (q, 12-Me), 15.9 (q, 2-Me), 10.5 (q, 15-Me), 9.9 (q, 4-Me), 9.1 (q, 10-Me). HRMS (ES) calcd for $C_{50}H_{78}N_2O_{13}$ (MH^+) 915.5504, found 915.5486. Anal. Calcd for $C_{50}H_{78}N_2O_{13}$: C, 65.62; H, 8.59; N, 3.06. Found: C, 65.84; H, 8.60; N, 3.02.

4.2.16.3. Preparation of 6-*O*-[3-(4′-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A (37c). To a solution of 6-*O*-allyl 8a-lactam **36**, (500 mg, 0.63 mmoL), palladium(II) acetate (28 mg, 0.125 mmoL), and tri(*o*-tolyl)phosphine (77 mg, 0.25 mmoL) in dry DMF (8 mL) were added 4-chloroquinoline (0.31 mL, 1.90 mmoL) and triethylamine (0.353 mL, 2.54 mmoL), and the mixture was flushed with argon. The reaction mixture was warmed to 70 °C for 2 h and stirred at 110 °C for 17 h. Additional palladium(II) acetate (28 mg, 0.125 mmoL), tri(*o*-tolyl)phosphine (77 mg, 0.25 mmoL), 4-chloroquinoline (0.31 mL, 1.90 mmoL), and triethylamine (0.353 mL, 2.54 mmoL) were added, and the mixture was stirred at 110 °C for an additional 20 h under argon. The solvent was evaporated under reduced pressure, and the crude residue was taken up in ethyl acetate, washed twice with aqueous saturated sodium bicarbonate, once with aqueous 2% tris(hydroxymethyl)aminomethane, and once with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (ethylacetate/*n*-hexane/diethylamine, 60:30:2) to give 406.4 mg (70%) of 6-*O*-[3-(4′-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A as a colorless solid: FAB-MS *m*/*z* 916 (MH^+, 94%); ^{1}H NMR ($CDCl_3$) δ 8.79 (d, 1H), 7.98 (d, 1H), 7.78 (m, 1H), 7.60 (m, 1H), 7.17 (d, 1H), 6.63 (d, 1H), 6.57 (m, 1H), 6.55 (d, 1H), 6.45 (d, 1H), 4.85 (1H, H-1″), 4.04 (dd, 2H), 3.97 (1H, H-5″), 2.91 (1H, H-4″), 2.80 (3H, 3″-OMe), 1.23 (3H, 5″-Me), 1.19 (3H, 3″-Me). ^{13}C NMR ($CDCl_3$) δ 180.1, 179.6, 150.0, 148.4, 146.8, 133.1, 129.6, 129.4, 128.8, 126.2, 124.0, 112.9, 76.8, 69.6. HRMS (ES) calcd for $C_{49}H_{77}N_3O_{13}$ (MH^+) 916.5456, found 916.5440. Anal. Calcd for $C_{49}H_{77}N_3O_{13}$: C, 64.24; H, 8.47; N, 4.59. Found: C, 64.45; H, 8.76; N, 4.41.

4.2.16.4. Synthesis of 6-*O*-[3-(3′-quinolyl)-2-propenyl]-9a-aza-9a-homoerythromycin A (39b). According to the same general procedure for the synthesis of **37b**, 200 mg of **38** (0.25 mmoL) afforded **39b** (155.6 mg, 67%) with the following structural characteristics: FAB-MS *m*/*z* 916 (MH^+, 85%); ^{1}H NMR ($CDCl_3$) δ 9.00 (d, 1H), 8.05 (d, 1H), 8.00 (d, 1H), 7.76 (d, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.43 (1H, 9a-CO*NH*), 6.57 (m, 1H, 6-OCH$_2$*CH*CHQ), 6.23 (d, 1H, 6-OCH$_2$CH*CH*Q), 4.90 (1H, H-1″), 4.00 (1H, H-5″), 3.91 (dd, 1H, 6-O*CH*$_2$CHCHQ), 3.00 (1H, H-4″), 2.84 (3H, 3″-OMe), 1.26 (3H, 5″-Me), 1.24 (3H, 3″-Me). HRMS (ES) calcd for $C_{49}H_{77}N_3O_{13}$ (MH^+) 916.5456, found 916.5443. Anal. Calcd for $C_{49}H_{77}N_3O_{13}$: C, 64.24; H, 8.47; N, 4.59. Found: C, 64.28; H, 8.52; N, 4.55.

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