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# Novel 9a,11-bridged azalides: One-pot synthesis of N′-substituted 2-imino-1,3-oxazolidines condensed to an azalide aglycone

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ABSTRACT

An efficient one-pot method for the synthesis of novel 9a,11-bridged 15-membered 9a-aza-9-deoxo-9a-homoerythromycin A and its 6-*O*-methyl analogue has been developed. The novel bicyclic azalide scaffold is characterized by an N′-substituted-2-imino-1,3-oxazolidine moiety bound to a macrolactone ring between positions 9a and 11. Removal of the cladinose sugar from the starting compounds allows easy preparation of a small series of such bicyclic 3-keto and 3,6-hemiketal azalide derivatives. A mechanism for the formation of N′-substituted-2-imino-1,3-oxazolidines is discussed. Antibacterial properties of the prepared compounds were evaluated.

## 1. Introduction

In order to improve the biological properties of standard antibacterial macrolides, bridging of the macrocyclic lactone ring appeared to be a very promising chemical transformation.[1] Some representatives of bicyclic macrolides have been progressed to the late clinical stage, for example, EDP-420, or to commercial applications, for example, dirithromycin and telithromycin (Fig. 1). These bridged structures are usually characterized by an additional attachment of various heteroalkyl or heteroaryl chains to a particular position on the bridge.

From a synthetic standpoint, modification of natural and semisynthetic macrolides is highly demanding due to the presence of a plethora of functional groups. Consequently, chemical transformations on macrolide scaffolds most often require interplay of specific protection/deprotection steps. Here we present a chemoselective and simple one-pot reaction that avoids the use of any protection/deprotection steps in the synthesis of a new class of bridged bicyclic macrolides, allowing an easy introduction of various substituents to the bridge.

## 2. Results and discussion

Our recent studies included research on novel 3-ketolides and 3,6-hemiketals of 15-membered azalides having the N-9a atom as part of an *urea moiety*.[2] In an attempt to prepare analogous 3-ketolides and 3,6-hemiketals with the N-9a atom as a part of a

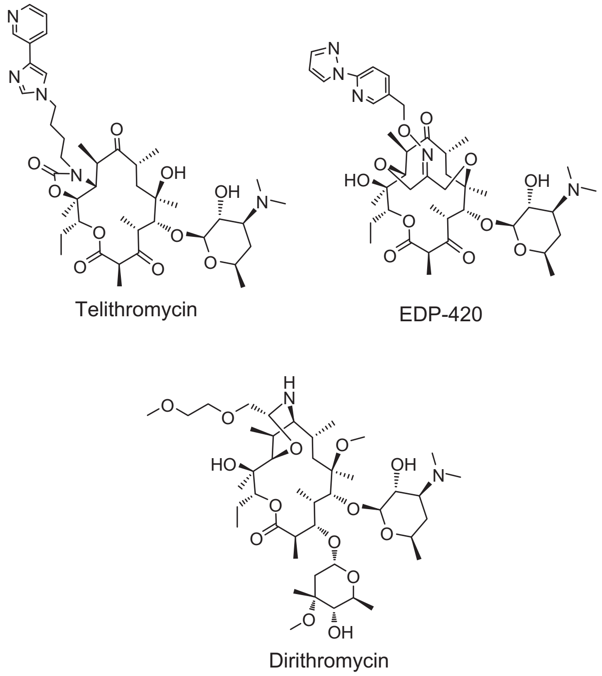

**Figure 1.** Some representatives of bicyclic antibacterial macrolides.

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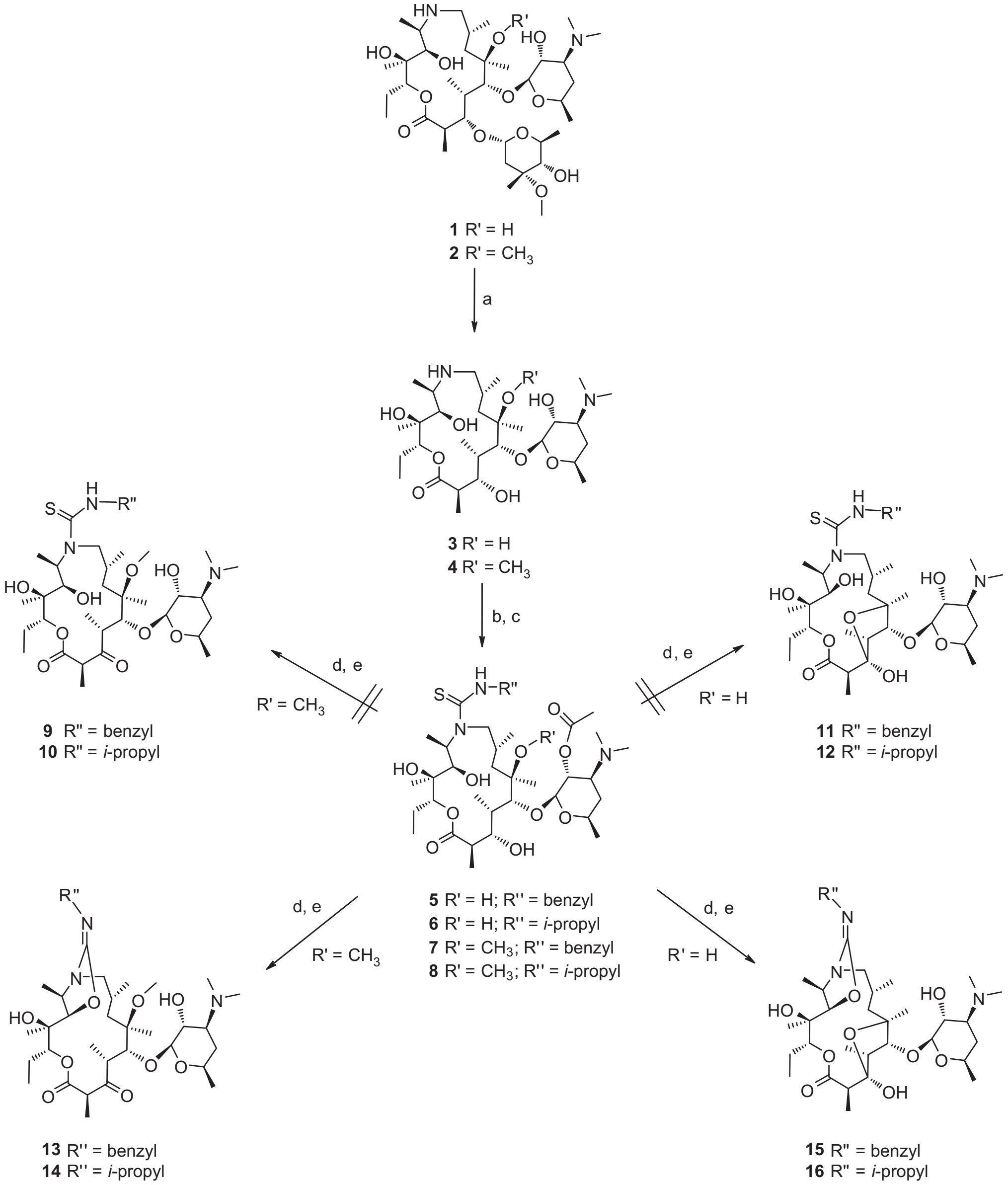
*thiourea unit* (9a-thiocarbamoyl derivatives), we synthesized benzyl and isopropyl thiourea derivatives of 3-decladinosyl-2′-acetyl-9a-aza-9-deoxo-9a-homoerythromycin A (**5** and **6**) and 3-decladinosyl-2′-acetyl-9a-aza-9-deoxo-6-*O*-methyl-9a-homoerythromycin A (**7** and **8**). Oxidation of the 3-hydroxy group of compounds **5** to **8** via the Pfitzner–Moffat procedure surprisingly afforded novel 9a,11-bridged-3-ketolides **13** and **14** and 9a,11-bridged-3,6-hemiketals **15** and **16** instead of the expected ketolides and hemiketals **9–12**, (Scheme 1). The reaction time-course (followed by HPLC-MS) revealed that formation of the 9a,11-bridge is faster than oxidation of the 3-OH group.

The N-9a, C-11 bridge of compounds **13**–**16** was identified by NMR and mass spectrometry as a five-membered 2-imino-1,3-oxazolidine system substituted at the N′-position. There was no occurrence of cyclizations to 12-OH or 6-OH, and only one imine stereoisomer was obtained.

Detailed MS/MS and NMR analysis of compound **15**, as a representative example, was performed in order to unambiguously determine its structure. The mass spectra of compound **15** show a molecular ion signal at *m*/*z* 690, 34 units less than the *m*/*z* of compound **11**. MS/MS spectra of this ion are also in agreement with structure **15**, showing a fragment of *m*/*z* 557 that corresponds to cleavage of the oxazolidine ring and elimination of benzyl isocyanate. A deuterium exchange experiment confirmed the presence of only three exchangeable hydrogen atoms in the molecule.

NMR analysis of compound **15** was consistent with the results obtained by MS/MS analysis. The oxygen bridge formed between atoms C-3 and C-6 was easily identified by significant carbon chemical shifts of 104.2 ppm (quaternary C-3) and 85.1 ppm (quaternary C-6), as well as shifts at 49.1 ppm (C-4) and 94.7 ppm (C-5). Characterization of the N-9a, C-11 bridge was more challenging although the presence of a quaternary carbon at 154.8 ppm (with HMBC correlation to the benzylic $CH_2$) indicated the appearance of a C=N double bond to which the benzyl group is attached. Since there were no other crosspeaks with this carbon in the HMBC spectrum, comparison of chemical shifts with similar compounds **1**–**4**[2] was performed. The biggest difference was observed in the carbon chemical shift of atom C-11 (downfield shift to 86.8 ppm) which



**Scheme 1.** Reagents and conditions:[2] (a) water/HCl, pH 1; (b) R″-SCN, TEA, toluene, 1–2 h; (c) acetic anhydride, $NaHCO_3$, dichloromethane, overnight; (d) EDC, dimethylsulfoxide, pyridinium trifluoroacetate, dichloromethane; (e) methanol, 24 h.

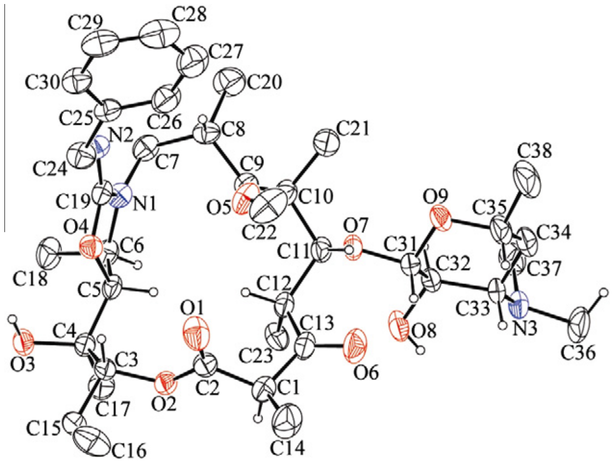


**Figure 2.** A view of the molecular structure of **13** with the atom labeling scheme. Thermal ellipsoids are shown at the 30% probability level. Hydrogen atoms and the water molecule are omitted for clarity.

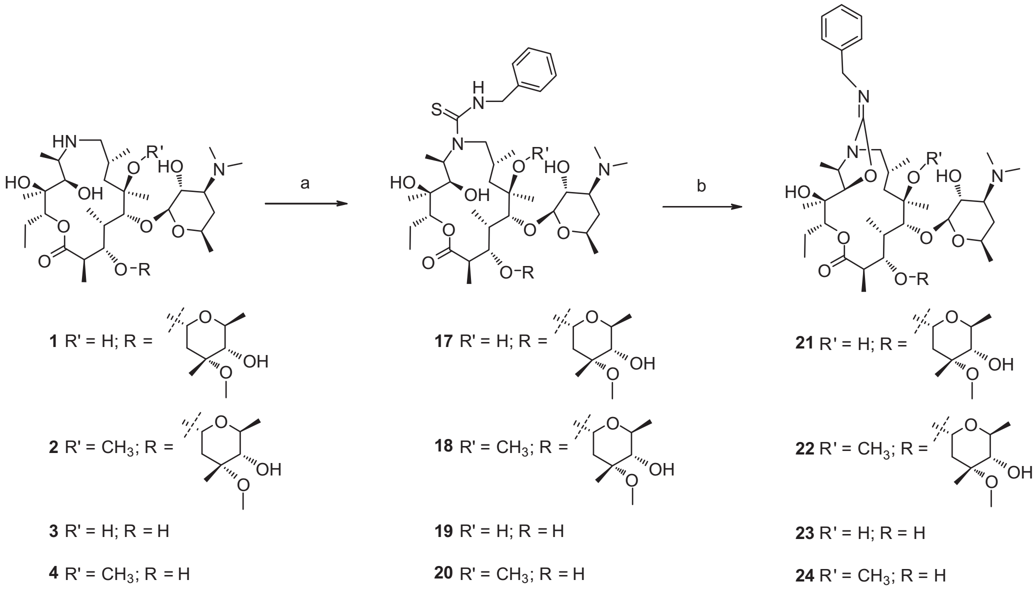
indicated that C-11 is directly involved in the formation of another ring on the macrocyclic lactone. Smaller differences in chemical shifts of carbons C-10 and 10-$CH_3$ suggested that these atoms are part of this ring as well. The coupling constant between H-10 and H-11 of **15** ($J_{10,11}$ = 5.1 Hz) is larger than in compounds **1**–**4** ($J_{10,11}$ <2 Hz), consistent with a conformational reorganization similar to that seen in azalides constrained via a five-membered 9a,11-cyclic carbamate ring.[3] The unusual downfield shifts of the 9-H protons and upfield carbon chemical shift of C-9, which are not part of the 1,3-oxazolidine ring, indicated the possible spatial vicinity of an imine nitrogen (C═N) electron pair that points toward the 9-$CH_2$ group. This is possible only if the imine double bond has the *Z*-configuration.

In order to confirm the conclusion above, a monocrystal of ketoazalide **13** was prepared and the crystal structure solved by X-ray analysis (Fig. 2). The molecular structure of **13** is characterized by the 15-membered macrolactone ring that is additionally constrained by introduction of the five-membered 2-imino-1,3-oxazolidine ring at positions 9a and 11. The *Z*-configuration of the imine double bond was unambiguously confirmed.

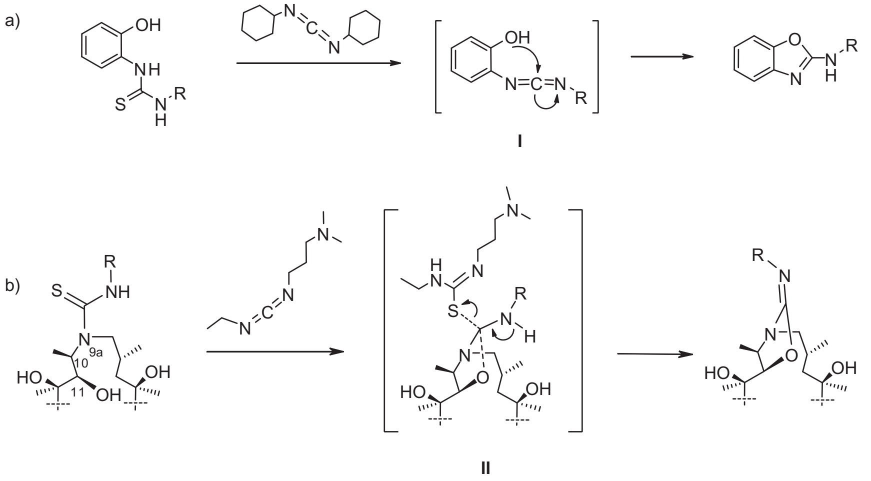
Having at hand this new bicyclic scaffold, we set our goal to optimize the reaction conditions and prepare a small series of new 9a,11-bridged azalides. Removal of dimethylsulfoxide and pyridinium trifluoroacetate from the Pfitzner–Moffat reagent mixture, and use of only EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) to react with unprotected 9a-thiocarbamoyl-3-decladinosyl derivatives **19** and **20** afforded exclusively the 9a,11-cyclic products **23** and **24**, respectively (Scheme 2). Although the reaction time time extended to over 3 days, protection of the 2′-OH group was not necessary. Increasing the reaction temperature to 40 °C shortened the reaction time to 24 h. Finally, chloroform as a solvent and a reaction temperature of 60 °C smoothly afforded solely the 9a,11-cyclized products **23** and **24** in 5 h and also allowed a decrease of EDC excess from 6 to 2 equiv. The same reaction conditions were applied to 9a-thiocarbamoyl azalides **17** and **18** to afford 9a,11-cyclic azalides **21** and **22**, respectively, without protection/deprotection of 2′-OH and 4″-OH.

Similar reactions of carbodiimides with thioureas were used for the formation of N,N-substituted guanidines[4,5] or cyclodesulfurization.[6] However, only thioureas derived from primary amines have been studied and the reaction mechanism involves formation of carbodiimides (**I**) as reactive intermediates (Scheme 3a). Since 9a-thiocarbamoyl derivatives **17**–**20** were prepared on the secondary amine, they cannot form carbodiimide intermediates in reaction with EDC. We propose the formation of the tetrahedral intermediate (**II**) that leads to five-membered ring closure (Scheme 3b).

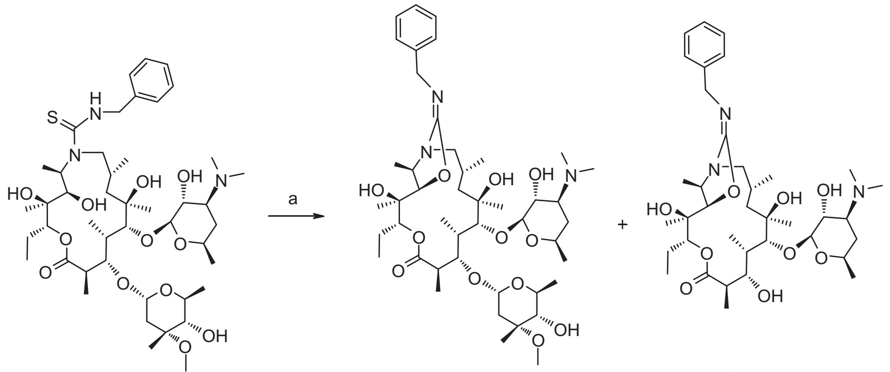
Polymer-supported carbodiimides[7] as well as the polymer-supported Mukaiyama reagent (*N*-methyl-2-chloropyridinium iodide)[8,9] were also successfully used for guanidine preparation. Since these polymer-supported reagents are commercially available we screened their usage in the synthesis of the 9a,11-iminooxazolidine **21**, which will allow the preparation of a series of 9a,11-oxazolidines in a high-throughput manner. Interestingly, formation of **21** was not observed when polymer-supported carbodiimides (PL-EDC or PL-DCC) were used (Scheme 4). On the other hand, the reaction using polymer-supported Mukaiyama reagent



**Scheme 2.** Optimization of reagents and conditions: (a) benzyl isothiocyanate, triethylamine, acetonitrile, 1–2 h; (b) EDC, dichloromethane, 3 days; or EDC, dichloromethane, 40 °C, 24 h; or EDC, chloroform, 60 °C, 5 h.



**Scheme 3.** The mechanism of the cyclodesulfurization reaction[5] versus the proposed reaction mechanism for the formation of 2-imino-1,3-oxazolidines.



**17** **21** **23**

| reagent | solvent | temp (°C) | time (h) | **21** | **23** |
|---|---|---|---|---|---|
| PL-EDC | DCM | 40 | 24 | 0 | 0 |
| PL-EDC | DMF | 60 | 24 | 0 | 0 |
| PL-DCC | DCM | 40 | 24 | 0 | 0 |
| PL-DCC | DMF | 60 | 24 | 0 | 0 |
| P-Mukaiyama | DCM | 40 | 24 | 0 | 40 |
| P-Mukaiyama | AcCN | 60 | 24 | 0 | 90 |
| P-Mukaiyama + TEA | AcCN | 60 | 4 | 90 | 0 |

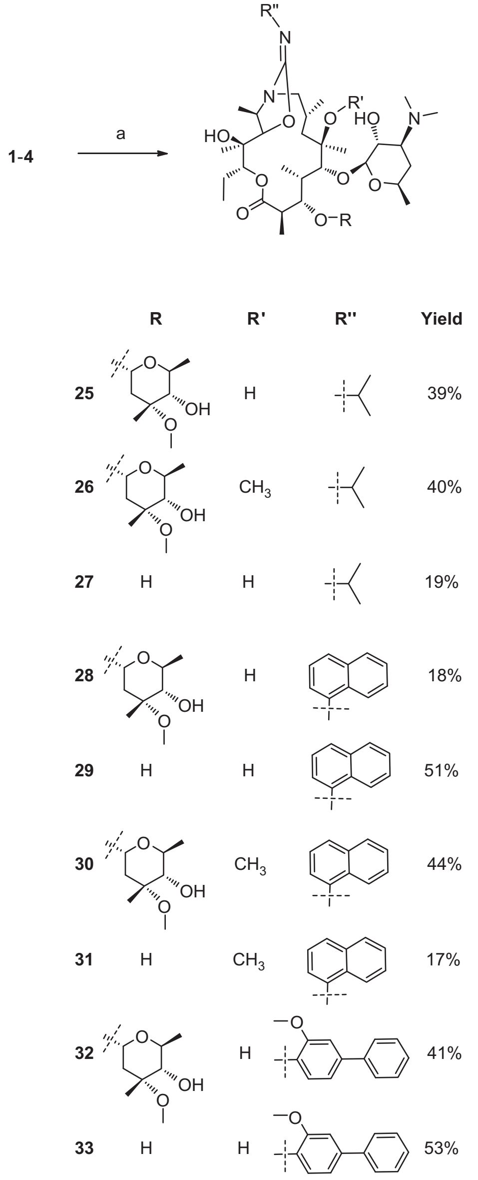
**Scheme 4.** Use of polymer-supported reagents. The ratios of **21** and **23** were determined by HPLC-MS.

in acetonitrile at 60 °C afforded complete conversion of **17** to **21** in only 4 h, but addition of an organic base was mandatory in order to prevent cladinose cleavage.

Since protection of the hydroxyl groups was not required for the 9a-thiocarbamoyl formation as well as during the 9a,11-cyclization step, we examined preparation of 9a,11-bridged macrolides in a one-pot two-step sequential manner. A reaction mixture of either **1** or **2** and benzyl isothiocyanate was stirred in acetonitrile at 60 °C. When the formation of 9a-thiocarbamoyl derivatives **17** or **18** was finished (determined by HPLC-MS), polymer-supported Mukaiyama reagent was added and heating at 60 °C continued until the formation of **21** or **22**, respectively, was completed. Encouraged by the efficiency of this approach, we also successfully applied one-pot multicomponent reaction conditions in which we added polymer supported Mukaiyama reagent together with benzyl isothiocyanate. The one-pot multicomponent reaction gave similar purities and yields as in two-step reactions.

The one-pot multicomponent procedure was used for the preparation of a small series of novel polycyclic 9a,11-bridged azalides having various substituents at the N′-position of the 2-imino-1,3-oxazolidine (Scheme 5). In all preparations only one imine geometric isomer was obtained. All new compounds have been characterized using NMR and mass spectrometry. Since the NMR data of all compounds show a similar pattern around the 'upper-left' part of macrolactone ring, we believe that the same imine *Z*-configuration is present in all prepared compounds. The yields after chromatographic purification are rather moderate, mainly because we insisted on very high purity of the final products. Nevertheless, to our knowledge this is the first example of successfully used polymer-supported reagent in a straightforward synthesis of such complex macrolide derivatives.

For all new compounds, the antibacterial activity was determined on a panel of various bacterial strains. MIC values for *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Haemophilus influenzae* strains are shown in Table 1. The 3-decladinosyl-6-hydroxy and 6-methoxy 9a,11-bridged azalides **23**, **24**, **27**, **29**, **31**, and **33** showed weak antibacterial activity against these strains, as did the 3-ketolides **13** and **14** and 3,6-hemiketals **15** and



**Scheme 5.** One-pot parallel synthesis using polymer supported Mukaiyama reagent: (a) R″-SCN, triethylamine, polymer supported Mukaiyama reagent, acetonitrile, 60 °C, overnight. Yields are given after chromatographic purification.

**16**. Macrolide compounds in which the cladinose was not removed showed much better antibacterial activity, particularly compounds **21**, **22**, **28**, **30**, and **32** that bear aromatic groups at the *N*′-atom of the oxazolidine ring. Interestingly, in these cases 6-hydroxy derivatives showed slightly better activity in comparison to 6-methoxy analogues (**21** vs **22** and **28** vs **30**). Importantly, all compounds show no effect on the eukaryotic organism *Saccharomyces cerevisiae*.

## 3. Conclusion

In conclusion, we described here an efficient one-pot procedure for the synthesis of a novel class of 9a,11-bridged 15-membered bicyclic azalides starting from 9a-aza-9-deoxo-9a-homoerythromycin A and its 6-*O*-methyl analogue. The procedure involves cyclization of intermediary-formed N′-substituted 9a-thicarbamoyl units into N′-substituted-2-imino-1,3-oxazolidine moieties condensed to the azalide scaffold between positions 9a and 11. Removal of the cladinose sugar from the starting compounds allows easy introduction of such substituted oxazolidine moieties to 3-keto and 3,6-hemiketal azalide derivatives. The steric constraint introduced into the macrolactone ring on 9a,11-bridging, and the stereoelectronic properties of the substituents on the *N*′-atom of the 2-imino group enable huge variation of physicochemical, hence biological properties of these new targets. The compounds in which *N*′-aryl-2-imino-1,3-oxazolidines were condensed to 9a-aza-9-deoxo-9a-homoerythromycin A showed promising antibacterial activities.

## 4. Experimental section

All solvents and reagents were used as supplied, unless noted otherwise. IR spectra were recorded on a Nicolet Magna-IR 760 FT-IR spectrometer (KBr). Mass spectra were recorded on a Varian MAT 311 instrument (FAB), and Platform LCZ or LCQ Deca instruments (ESI). HRMS (ESI) were recorded on a Micromass Qtof2. NMR spectra were recorded at 25 °C in $CDCl_3$ with TMS as the internal standard on Bruker Avance DRX500 and Bruker Avance III 600 spectrometers, equipped with 5 mm diameter inverse detection probes with *z*-gradient accessories, as well as a Bruker Avance DPX300 spectrometer using a dual $^1H/^{13}C$ probe. For characterization of complex organic structures one-dimensional (1D) ($^1H$ and APT) and two-dimensional (2D) (COSY, HMQC and HMBC) NMR techniques were used.

### 4.1. Preparation of 9a,11-bridged 3-ketolides (13 and 14) and 3,6-hemiketals (15 and 16)

*General procedure*: To a solution of **5–8**[2] in dichloromethane (*c* 0.05 g/ml), DMSO (12 equiv) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 6 equiv) were added. The reaction mixture was cooled to 15 °C and a solution of pyridinium trifluoroacetate (6 equiv) in dichloromethane (*c* 0.2 g/ml) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 2 h. Into the reaction mixture brine was added and the pH was adjusted to 9.5. The layers were separated and the aqueous layer extracted two more times with dichloromethane. The combined organic extracts were rinsed with brine, saturated aqueous $NaHCO_3$ solution and water, dried over $K_2CO_3$ and evaporated, yielding a crude product which was dissolved in MeOH (*c* 0.02 g/ml) and stirred for 24 h at room temperature. The solvent was evaporated and the residue purified by low pressure chromatography on a silica gel column using the system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:3:0.3) as eluents to afford **13**–**16**.

**Table 1**
Antibacterial activity of the prepared macrolides

| Strain | MIC (μg/ml) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **13** | **14** | **15** | **16** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** | **33** |
| *S. aureus* | >64 | >64 | >64 | >64 | 2 | 16 | 64 | >64 | 16 | 16 | >64 | 8 | >64 | 16 | >64 | 2 | >64 |
| *S. pneumoniae* | 2 | 16 | 32 | 16 | <0.125 | <0.125 | 8 | 32 | 2 | 0.5 | 4 | <0.125 | >64 | 0.5 | 64 | <0.125 | >64 |
| *S. pyogenes* | 8 | >64 | 32 | 32 | <0.125 | <0.125 | 8 | 16 | 2 | 1 | 8 | 0.25 | >64 | 1 | >64 | <0.125 | >64 |
| *M. catarrhalis* | 8 | 16 | 32 | 32 | 2 | 4 | 64 | >64 | 16 | 2 | >64 | 4 | 64 | 8 | 16 | 8 | 32 |
| *H. influenzae* | >64 | >64 | >64 | >64 | 16 | 32 | >64 | >64 | >64 | 64 | >64 | 8 | >64 | 32 | >64 | 8 | >64 |

### 4.2. 9a,11-*O*-(*N*′-Benzylcarbonimidoyl)-3-decladinosyl-3-keto-6-*O*-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (13)

According to the general procedure 1.93 g of **7** (1.68 mmol) afforded **13** (541 mg, 39%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3444, 2973, 2938, 2876, 2824, 2786, 1743, 1713, 1455, 1407, 1379, 1351, 1335, 1297, 1255, 1166, 1111, 1075, 1052, 1003, 982, 940, 915, 893, 834, 733, 699, 667, 617. $^1$H NMR (500 MHz, CDCl$_3$) [$\delta$/ppm] *benzyl*: 7.36 (2 × CH), 7.28 (2 × CH), 7.17 (CH), 4.50 (CH$_2$); *macrolide*: 5.16 (13-H), 4.50 (5-H), 4.38 (1′-H), 4.33 (11-H), 3.77 (2-H), 3.63 (5′-H), 3.49 (9-H$_a$), 3.48 (10-H), 3.33 (4-H), 3.22 (2′-H), 2.83 (6-OCH$_3$), 2.57 (8-H), 2.48 (3′-H), 2.27 (9-H$_b$), 2.26 (3′-N(CH$_3$)$_2$), 1.96 (14-H$_a$), 1.67 (4′-H$_a$), 1.56 (14-H$_b$), 1.37 (2-CH$_3$), 1.35 (4-CH$_3$), 1.33 (7-H$_a$), 1.31 (7-H$_b$), 1.28 (6-CH$_3$), 1.28 (12-CH$_3$), 1.27 (5′-CH$_3$), 1.25 (4′-H$_b$), 1.20 (10-CH$_3$), 0.94 (8-CH$_3$), 0.91 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [$\delta$/ppm] *benzyl*: 143.0 (C), 127.8 (2 × CH), 127.1 (2 × CH), 125.6 (CH), 50.1 (CH$_2$); *macrolide*: 206.8 (C-3), 170.6 (C-1), 150.9 (C=N), 102.6 (C-1′), 78.8 (C-11), 77.7 (C-6), 76.9 (C-13), 76.0 (C-5), 71.7 (C-12), 70.2 (C-2′), 69.3 (C-5′), 65.8 (C-3′), 58.9 (C-10), 50.5 (C-9), 49.9 (6-OCH$_3$), 49.9 (C-2), 44.7 (4-C), 37.2 (C-7), 40.2 (3′-N(CH$_3$)$_2$), 28.4 (C-4′), 24.6 (8-C), 21.2 (5′-CH$_3$), 20.7 (C-14), 20.4 (8-CH$_3$), 19.2 (6-CH$_3$), 14.2 (10-CH$_3$), 15.4 (12-CH$_3$), 13.9 (2-CH$_3$), 13.2 (4-CH$_3$), 10.4 (C-15). HRMS (ES) calcd for C$_{38}$ H$_{61}$N$_3$O$_9$ (M+H$^+$) 704.4498, found 704.4486.

### 4.3. 9a,11-*O*-(*N*′-Isopropylcarbonimidoyl)-3-decladinosyl-3-keto-6-*O*-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (14)

According to the general procedure 1.52 g of **8** (2.67 mmol) afforded **14** (175 mg, 10%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3564, 3445, 2972, 2938, 2877, 2833, 2787, 1742, 1709, 1456, 1403, 1379, 1360, 1336, 1296, 1254, 1213, 1165, 1110, 1074, 1058, 1000, 982, 939, 916, 893, 836, 743, 717, 673. $^1$H NMR (500 MHz, CDCl$_3$) [$\delta$/ppm] *isopropyl*: 3.74 (CH), 1.11 (2 × CH$_3$); *macrolide*: 5.20 (13-H), 4.51 (5-H), 4.35 (1′-H), 4.25 (11-H), 3.76 (2-H), 3.62 (5′-H), 3.44 (9-H$_a$), 3.40 (10-H), 3.29 (4-H), 3.21 (2′-H), 2.89 (6-OCH$_3$), 2.47 (3′-H), 2.45 (8-H), 2.26 (3′-N(CH$_3$)$_2$), 2.21 (9-H$_b$), 2.02 (14-H$_a$), 1.59 (14-H$_b$), 1.48 (4′-H$_a$), 1.36 (2-CH$_3$), 1.32 (4-CH$_3$), 1.29 (12-CH$_3$), 1.26 (5′-CH$_3$), 1.25 (7-H$_a$), 1.23 (7-H$_b$), 1.23 (6-CH$_3$), 1.23 (4′-H$_b$), 1.19 (10-CH$_3$), 0.89 (8-CH$_3$), 0.92 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [$\delta$/ppm] *isopropyl*: 50.0 (CH), 25.0 (2 × CH$_3$); *macrolide*: 206.8 (C-3), 170.7 (C-1), 148.2 (C=N), 102.6 (C-1′), 78.5 (C-11), 77.5 (C-6), 77.4 (C-13), 75.9 (C-5), 71.8 (C-12), 70.2 (C-2′), 69.3 (C-5′), 65.8 (C-3′), 58.4 (C-10), 50.5 (C-9), 49.6 (6-OCH$_3$), 46.5 (C-2), 44.7 (4-C), 37.1 (C-7), 40.2 (3′-N(CH$_3$)$_2$), 28.2 (C-4′), 24.1 (8-C), 21.2 (5′-CH$_3$), 20.8 (C-14), 20.3 (8-CH$_3$), 19.5 (6-CH$_3$), 14.1 (10-CH$_3$), 15.5 (12-CH$_3$), 14.1 (2-CH$_3$), 13.2 (4-CH$_3$), 10.3 (C-15). HRMS (ES) calcd for C$_{34}$ H$_{61}$N$_3$O$_9$ (M+H$^+$) 656.4486, found 656.4506.

### 4.4. 9a,11-*O*-(*N*′-Benzylcarbonimidoyl)-3-decladinosyl-3,6-hemiketal-9-deoxo-9a-aza-9a-homoerythromycin A (15)

According to the general procedure 200 mg of **5** (0.26 mmol) afforded **15** (81 mg, 45%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3487, 2974, 2936, 2877, 2789, 1722, 1688, 1457, 1382, 1252, 1190, 1170, 1113, 1079, 1046, 1009, 967, 913, 835, 733, 699. $^1$H NMR (500 MHz, CDCl$_3$) [$\delta$/ppm] *benzyl*: 7.31 (4xCH), 7.21 (CH), 4.41 and 4.35 (CH$_2$); *macrolide*: 4.76 (13-H), 4.15 (11-H), 4.14 (1′-H), 3.58 (5-H), 3.54 (5′-H), 3.41 (9-H$_a$), 3.13 (2′-H), 2.81 (9-H$_b$), 2.64 (2-H), 2.57 (3′-H), 2.28 (3′-N(CH$_3$)$_2$), 2.05 (4-H), 1.92 (14-H$_a$), 1.81 (7-H$_a$), 1.74 (8-H), 1.66 (4′-H$_a$), 1.57 (7-H$_b$), 1.45 (14-H$_b$), 1.32 (6-CH$_3$), 1.22 (2-CH$_3$), 1.20 (12-CH$_3$), 1.15 (4′-H$_b$), 1.14 (4-CH$_3$), 1.13 (5′-CH$_3$), 1.08 (10-CH$_3$), 0.95 (8-CH$_3$), 0.82 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [$\delta$/ppm] *benzyl*: 141.2 (C), 128.0 (2 × CH), 127.4 (2 × CH), 126.3 (CH), 48.4 (CH$_2$); *macrolide*: 175.6 (C-1), 154.8 (C=N), 106.2 (C-1′), 104.2 (C-3), 94.7 (C-5), 85.1 (C-6), 86.6 (C-11), 77.4 (C-13), 74.3 (C-12), 69.5 (C-2′), 68.4 (C-5′), 64.4 (C-3′), 54.4 (C-10), 49.3 (C-9), 49.2 (C-2), 49.1 (4-C), 43.4 (C-7), 40.3 (3′-N(CH$_3$)$_2$), 30.6 (C-4′), 29.6 (8-C), 25.5 (6-CH$_3$), 23.8 (8-CH$_3$), 21.2 (C-14), 21.1 (5′-CH$_3$), 16.7 (12-CH$_3$), 16.7 (12-CH$_3$), 11.9 (10-CH$_3$), 14.3 (2-CH$_3$), 13.5 (4-CH$_3$), 10.6 (C-15). HRMS (ES) calcd for C$_{37}$ H$_{59}$N$_3$O$_9$ (M+H$^+$) 690.4324, found 690.4315.

### 4.5. 9a,11-*O*-(*N*′-Isopropylcarbonimidoyl)-3-decladinosyl-3,6-hemiketal-9-deoxo-9a-aza-9a-homoerythromycin A (16)

According to the general procedure 1.24 g of **6** (1.73 mmol) afforded **16** (131 mg, 16%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3493, 2973, 2937, 2897, 2788, 1726, 1693, 1456, 1411, 1382, 1360, 1336, 1254, 1168, 1114, 1079, 1044, 1010, 968, 914, 868, 835, 792, 756, 717, 681, 646. $^1$H NMR (500 MHz, CDCl$_3$) [$\delta$/ppm] *isopropyl*: 3.72 (CH), 1.09 (2 × CH$_3$); *macrolide*: 4.94 (13-H), 4.38 (10-H), 4.21 (1′-H), 4.11 (11-H), 3.70 (5-H), 3.51 (5′-H), 3.43 (9-H$_a$), 3.25 (2′-H), 2.73 (9-H$_b$), 2.56 (2-H), 2.48 (3′-H), 2.29 (3′-N(CH$_3$)$_2$), 2.12 (4-H), 1.95 (14-H$_a$), 1.84 (8-H), 1.79 (7-H$_a$), 1.67 (4′-H$_a$), 1.62 (7-H$_b$), 1.51 (14-H$_b$), 1.39 (6-CH$_3$), 1.34 (12-CH$_3$), 1.28 (2-CH$_3$), 1.28 (4′-H$_b$), 1.26 (4-CH$_3$), 1.22 (5′-CH$_3$), 1.03 (10-CH$_3$), 1.01 (8-CH$_3$), 0.90 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [$\delta$/ppm] *isopropyl*: 46.3 (CH), 24.9 (2 × CH$_3$); *macrolide*: 175.5 (C-1), 150.3 (C=N), 105.6 (C-1′), 103.5 (C-3), 94.9 (C-5), 84.8 (C-6), 84.7 (C-11), 77.7 (C-13), 74.2 (C-12), 69.7 (C-2′), 69.6 (C-5′), 65.5 (C-3′), 52.2 (C-10), 49.8 (C-2), 49.8 (4-C), 49.6 (C-9), 43.9 (C-7), 40.2 (3′-N(CH$_3$)$_2$), 30.4 (8-C), 28.2 (C-4′), 25.5 (6-CH$_3$), 24.0 (8-CH$_3$), 21.8 (C-14), 21.1 (5′-CH$_3$), 17.5 (12-CH$_3$), 14.1 (2-CH$_3$), 13.9 (4-CH$_3$), 11.8 (10-CH$_3$), 10.4 (C-15). HRMS (ES) calcd for C$_{33}$ H$_{59}$N$_3$O$_9$ (M+H$^+$) 642.4320, found 642.4330.

### 4.6. Preparation of 9a-(*N*′-benzylthiocarbamoyl)- and 9a-(*N*′-benzylthiocarbamoyl)-3-decladinosyl derivatives (17–20)

*General procedure*: To the solution of compound **1–4** in acetonitrile (*c* 0.05 g/ml), benzyl isothiocyanate (3 equiv) and triethylamine (3 equiv) were added. The reaction mixture was stirred at 60 °C for 3 h. After removal of the solvent under reduced pressure, a crude residue was obtained which was used as-is for further reactions. Purification of the crude products by solid phase extraction techniques (SPE), solvent system gradient (98–95% CH$_2$Cl$_2$/(CH$_3$OH/NH$_4$OH = 9:1.5)), afforded pure products **17** to **20** for the purpose of structure confirmation.

### 4.7. 9-Deoxo-9-dihydro-9a-(*N*′-benzylthiocarbamoyl)-9a-aza-9a-homoerythromycin A (17)

According to the general procedure 5.0 g of **1** (6.8 mmol) afforded **17** (5.56 g, 92%) as a white foam. Analytical data for the purified sample: $^1$H NMR (600 MHz, CDCl$_3$) [$\delta$/ppm] *benzyl*: 7.36 (2 × CH), 7.31 (2 × CH), 7.26 (CH), 4.85 and 4.68 (CH$_2$); *macrolide*: 4.85 (1″-H), 4.71 (13-H), 4.38 (1′-H), 4.08 (3-H), 4.03 (5″-H), 3.80 (11-H), 3.48 (5′-H), 3.46 (5-H), 3.27 (3″-OCH$_3$), 3.24 (2′-H), 2.99 (4″-H), 2.83 (2-H), 2.46 (3′-H), 2.32 (2″-H$_a$), 2.26 (3′-N(CH$_3$)$_2$), 2.11 (8-H), 1.87 (14-H$_a$), 1.82 (4-H), 1.64 (4′-H$_a$), 1.53 (2″-H$_b$), 1.49 (14-H$_b$), 1.36 (6-CH$_3$), 1.29 (5″-CH$_3$), 1.29 (12-CH$_3$), 1.28 (10-CH$_3$), 1.22 (2-CH$_3$), 1.21 (5′-CH$_3$), 1.21 (4′-H$_b$), 1.18 (3″-CH$_3$), 1.07 (4-CH$_3$), 0.92 (8-CH$_3$), 0.87 (15-H). $^{13}$C NMR (150 MHz, CDCl$_3$) [$\delta$/ppm] *benzyl*: 138.0 (CH), 128.6 (2 × CH), 128.4 (2 × CH), 126.8 (CH) 50.8 (CH$_2$); *macrolide*: 183.5 (9a-N(C=S)NH), 177.9 (C-1), 103.7 (C-1′), 96.1 (1″-C), 85.6 (C-5), 79.8 (C-3), 78.2 (C-13), 77.9 (4″-C), 75.8 (C-6), 74.6 (C-12), 72.8 (C-11), 72.6 (3″-C), 71.0 (C-2′), 69.0 (C-5′), 65.7 (5″-C), 65.1 (C-3′), 56.8 (C-10), 57.2 (C-9), 49.4 (3″-OCH$_3$), 45.6 (C-2), 40.5 (4-C), 40.4 (3′-

$N(CH_3)_2$), 34.9 (2″-C), 29.3 (C-4′), 27.8 (8-C), 27.2 (6-$CH_3$), 21.8 (C-14), 21.6 (3″-$CH_3$), 21.3 (8-$CH_3$), 21.1 (5′-$CH_3$), 18.6 (5″-$CH_3$), 17.0 (12-$CH_3$), 15.8 (2-$CH_3$), 13.3 (10-$CH_3$), 11.4 (C-15), 9.8 (4-$CH_3$). HRMS (ES) calcd for $C_{45}H_{78}N_3O_{12}S$ (M+H$^+$) 884.5306, found 884.5301.

### 4.8. 9-Deoxo-9-dihydro-9a-(*N*′-benzylthiocarbamoyl)-6-*O*-methyl-9a-aza-9a-homoerythromycin A (18)

According to the general procedure 1.26 g of **2** (1.68 mol) afforded **18** (1.38 g, 92%) as a white foam. Analytical data for the purified sample:$^1$H NMR (600 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 7.38 (2 × CH), 7.31 (2 × CH), 7.27 (CH), 4.86 and 4.70 ($CH_2$); *macrolide*: 4.91 (1″-H), 4.47 (1′-H), 3.94 (3-H), 4.01 (5″-H), 3.89 (11-H), 3.69 (5-H), 3.51 (5′-H), 3.31 (3″-$OCH_3$), 3.24 (6-$OCH_3$), 3.18 (2′-H), 3.01 (4″-H), 2.63 (2-H), 2.42 (3′-H), 2.32 (2″-$H_a$), 2.28 (3′-$N(CH_3)_2$), 2.21 (8-H), 1.86 (14-$H_a$), 1.73 (4-H), 1.64 (4′-$H_a$), 1.57 (2″-$H_b$), 1.49 (14-$H_b$), 1.34 (6-$CH_3$), 1.30 (10-$CH_3$), 1.28 (2-$CH_3$), 1.26 (5″-$CH_3$), 1.23 (5′-$CH_3$), 1.21 (4′-$H_b$), 1.18 (12-$CH_3$), 1.18 (3″-$CH_3$), 1.07 (4-$CH_3$), 0.88 (8-$CH_3$), 0.86 (15-H). $^{13}$C NMR (150 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 138.0 (C), 128.7 (4xCH) and 127.8 (CH), 51.2 ($CH_2$); *macrolide*: 176.9 (9a-N(C=S)NH), 176.2 (C-1), 102.6 (C-1′), 95.8 (1″-C), 89.8 (C-5), 79.8 (C-6), 78.8 (C-3), 77.9 (4″-C), 72.0 (C-11), 72.8 (3″-C), 68.6 (C-2′), 68.6 (C-5′), 65.8 (5″-C), 65.5 (C-3′), 57.1 (C-10), 51.1 (6-$OCH_3$), 49.4 (3″-$OCH_3$), 44.5 (C-2), 36.9 (4-C), 40.4 (3′-$N(CH_3)_2$), 34.9 (2″-C), 28.2 (C-4′), 26.8 (8-C), 22.2 (C-14), 21.6 (3″-$CH_3$), 21.2 (6-$CH_3$), 21.3 (8-$CH_3$), 21.5 (5′-$CH_3$), 18.6 (5″-$CH_3$), 16.8 (12-$CH_3$), 15.3 (2-$CH_3$), 12.8 (10-$CH_3$), 11.4 (C-15), 9.3 (4-$CH_3$). HRMS (ES) calcd for $C_{46}H_{80}N_3O_{12}S$ (M+H$^+$) 898.5463, found 898.5469.

### 4.9. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-benzylthiocarbamoyl)-9a-aza-9a-homoerythromycin A (19)[2]

According to the general procedure 2 g of **3** (3.46 mmol) afforded **19** (2.17 g, 94%) as a white foam.

### 4.10. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-benzylthiocarbamoyl)-6-*O*-methyl-9a-aza-9a-homoerythromycin A (20)

According to the general procedure 75 mg of **4** (0.127 mmol) afforded **20** (85 mg, 91%) as a white foam. $^1$H NMR (600 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 7.37 (2 × CH), 7.32 (2 × CH), 7.27 (CH), 4.78 and 4.69 ($CH_2$); *macrolide*: 4.94 (13-H), 4.37 (1′-H), 3.69 (3-H), 3.66 (5-H), 3.65 (11-H), 3.51 (5′-H), 3.23 (2′-H), 3.12 (6-$OCH_3$), 2.63 (2-H), 2.46 (3′-H), 2.23 (3′-$N(CH_3)_2$), 2.18 (8-H), 1.87 (14-$H_a$), 1.72 (4-H), 1.65 (4′-$H_a$), 1.49 (7-$H_a$), 1.49 (14-$H_b$), 1.33 (12-$CH_3$), 1.30 (6-$CH_3$), 1.25 (10-$CH_3$), 1.25 (2-$CH_3$), 1.23 (5′-$CH_3$), 1.22 (4′-$H_b$), 1.17 (7-$H_b$), 1.07 (4-$CH_3$), 0.88 (15-H), 0.87 (8-$CH_3$). $^{13}$C NMR (150 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 138.0 (C), 128.8 (4xCH), 127.7 (CH), 51.2 ($CH_2$); *macrolide*: 176.2 (9a-N(C=S)NH), 176.2 (C-1), 106.8 (C-1′), 89.0 (C-5), 79.8 (C-6), 76.2 (C-13), 72.2 (C-3), 72.2 (C-11), 70.6 (C-2′), 70.1 (C-5′), 65.7 (C-3′), 56.5 (C-10), 49.9 (6-$OCH_3$), 44.6 (C-2), 40.3 (3′-$N(CH_3)_2$), 36.9 (4-C), 28.1 (C-4′), 26.6 (8-C), 22.3 (C-14), 21.2 (6-$CH_3$), 21.2 (8-$CH_3$), 21.2 (5′-$CH_3$), 16.8 (12-$CH_3$), 15.2 (2-$CH_3$), 13.0 (10-$CH_3$), 11.5 (C-15), 8.1 (4-$CH_3$). HRMS (ES) calcd for $C_{38}H_{66}N_3O_9S$ (M+H$^+$) 740.4520, found 740.4523.

### 4.11. Cyclization of *N*′-benzyl thioureas 17–20 using EDC

*General procedure*: To a solution of 9a-(*N*′-benzylthiocarbamoyl) derivatives **17**–**20** in chloroform (*c* 0.05 g/ml), EDC (2 equiv) was added. The reaction mixture was stirred at 60 °C overnight. The reaction mixture was washed with saturated $NaHCO_3$, brine, water, and dried over $K_2CO_3$. After evaporation of the solvent, the crude product was purified on the Flashmaster II—solid phase extraction techniques (SPE). Solvent system gradient (98–95% $CH_2Cl_2$/($CH_3OH/NH_4OH = 9:1.5$)) and 8 ml/min flow rate was used. The combining and evaporating of chromatographically homogenous fractions gave the title product.

### 4.12. 9a,11-*O*-(*N*′-Benzylcarbonimidoyl)-9-deoxo-9a-aza-9a-homoerythromycin A (21)

According to the general procedure 3.0 g of **17** (3.4 mmol) afforded **21** (1.05 g, 37%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3572, 3452, 2971, 2935, 2879, 1739, 1688, 1457, 1410, 1379, 1354, 1257, 1165, 1111, 1052, 1003, 960, 896, 865, 834, 732, 701, 673, 638. $^1$H NMR (500 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 7.47 (2 × CH), 7.31 (2 × CH), 7.20 (CH), 4.49 ($CH_2$); *macrolide*: 5.07 (13-H), 4.92 (1″-H), 4.38 (1′-H), 4.26 (11-H), 4.08 (3-H), 4.02 (5″-H), 3.71 (9-$H_a$), 3.57 (5-H), 3.56 (10-H), 3.48 (5′-H), 3.30 (3″-$OCH_3$), 3.20 (2′-H), 3.04 (4″-H), 2.92 (2-H), 2.44 (3′-H), 2.38 (9-$H_b$), 2.37 (8-H), 2.37 (2″-$H_a$), 2.28 (3′-$N(CH_3)_2$), 1.96 (4-H), 1.89 (14-$H_a$), 1.52 (7-$H_a$), 1.66 (4′-$H_a$), 1.65 (2″-$H_b$), 1.51 (14-$H_b$), 1.31 (5″-$CH_3$), 1.29 (7-$H_b$), 1.26 (4′-$H_b$), 1.25 (2-$CH_3$), 1.25 (3″-$CH_3$), 1.22 (6-$CH_3$), 1.21 (5′-$CH_3$), 1.21 (10-$CH_3$), 1.15 (12-$CH_3$), 1.07 (4-$CH_3$), 0.98 (8-$CH_3$), 0.91 (15-H). $^{13}$C NMR (125 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 141.5 (C), 128.3 (4xCH), 126.4 (CH), 49.5 ($CH_2$); *macrolide*: 174.4 (C-1), 154.6 (C=N), 103.2 (C-1′), 96.8 (C-1″), 83.9 (C-5), 80.6 (C-11), 80.6 (C-3), 78.2 (C-6), 78.0 (4″-C), 75.9 (C-13), 72.7 (C-3″), 71.9 (C-12), 71.0 (C-2′), 68.8 (C-5′), 65.7 (C-5″), 65.6 (C-3′), 59.4 (C-10), 50.4 (C-9), 49.4 (3″-$OCH_3$), 44.8 (C-2), 39.3 (4-C), 37.1 (C-7), 40.3 (3′-$N(CH_3)_2$), 35.3 (2″-C), 28.7 (C-4′), 26.9 (6-$CH_3$), 24.6 (8-C), 21.5 (3″-$CH_3$), 21.0 (8-$CH_3$), 20.6 (C-14), 21.3 (5′-$CH_3$), 18.6 (5″-$CH_3$), 16.7 (2-$CH_3$), 15.4 (12-$CH_3$), 14.1 (10-$CH_3$), 9.4 (4-$CH_3$), 10.6 (C-15). HRMS (ES) calcd for $C_{45}\,H_{75}N_3O_{12}$ (M+H$^+$) 850.5424, found 850.5149.

### 4.13. 9a,11-*O*-(*N*′-Benzylcarbonimidoyl)-6-*O*-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (22)

According to the general procedure 120 mg of **18** (0.12 mmol) afforded **22** (45 mg, 43%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3451, 2972, 2936, 1739, 1683, 1461, 1409, 1378, 1362, 1294, 1265, 1212, 1164, 1112, 1085, 1053, 1004, 940, 903, 834, 733, 700, 673, 639. $^1$H NMR (500 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 7.39 (2 × CH), 7.28 (2 × CH), 7.16 (CH), 4.52 ($CH_2$); *macrolide*: 5.07 (13-H), 4.94 (1″-H), 4.48 (1′-H), 4.12 (11-H), 3.47 (9-$H_a$), 4.07 (5″-H), 3.89 (3-H), 3.78 (5-H), 3.52 (5′-H), 3.47 (10-H), 3.32 (3″-$OCH_3$), 3.23 (2′-H), 3.19 (6-$OCH_3$), 3.04 (4″-H), 2.95 (2-H), 2.52 (8-H), 2.43 (3′-H), 2.35 (2″-$H_a$), 2.29 (3′-$N(CH_3)_2$), 2.25 (9-$H_b$), 2.10 (4-H), 1.88 (14-$H_a$), 1.64 (4′-$H_a$), 1.60 (2″-$H_b$), 1.50 (14-$H_b$), 1.39 (7-$H_a$), 1.35 (5″-$CH_3$), 1.31 (2-$CH_3$), 1.28 (7-$H_b$), 1.26 (4′-$H_b$), 1.24 (6-$CH_3$), 1.24 (3″-$CH_3$), 1.22 (5′-$CH_3$), 1.17 (10-$CH_3$), 1.17 (12-$CH_3$), 1.07 (4-$CH_3$), 0.95 (8-$CH_3$), 0.87 (15-H). $^{13}$C NMR (125 MHz, DMSO) [$\delta$/ppm] *benzyl*: 143.0 (C), 127.8 (2 × CH), 127.3 (2 × CH), 125.6 (CH), 50.2 ($CH_2$); *macrolide*: 174.1 (C-1), 151.5 (C=N), 102.3 (C-1′), 96.5 (C-1″), 80.8 (C-5), 79.4 (C-3), 78.8 (C-11), 78.6 (C-6), 77.8 (C-4″), 75.9 (C-13), 72.7 (C-3″), 71.8 (C-12), 71.0 (C-2′), 68.4 (C-5′), 65.9 (C-5″), 65.5 (C-3′), 58.5 (C-10), 50.2 (C-9), 49.3 (3″-$OCH_3$), 44.7 (C-2), 40.2 (3′-$N(CH_3)_2$), 38.0 (4-C), 36.3 (C-7), 35.2 (2″-C), 28.5 (C-4′), 24.7 (8-C), 21.4 (5′-$CH_3$), 21.4 (3″-$CH_3$), 20.6 (8-$CH_3$), 20.3 (5″-$CH_3$), 20.3 (C-14), 18.6 (6-$CH_3$), 16.8 (2-$CH_3$), 14.0 (10-$CH_3$), 15.1 (12-$CH_3$), 10.3 (C-15), 9.3 (4-$CH_3$). HRMS (ES) calcd for $C_{45}\,H_{75}N_3O_{12}$ (M+H$^+$) 864.5580, found 864.5585.

### 4.14. 9a,11-*O*-(*N*′-Benzylcarbonimidoyl)-3-decladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A (23)

According to the general procedure 100 mg of **19** (0.14 mmol) afforded **23** (28 mg, 29%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]:

3448, 2971, 2935, 2877, 1737, 1688, 1525, 1457, 1412, 1379, 1353, 1258, 1163, 1112, 1076, 1048, 1003, 964, 895, 834, 733, 700, 673. $^1$H NMR (500 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 7.40 (2 × CH), 7.29 (2 × CH), 7.18 (CH), 4.48 ($CH_2$); *macrolide*: 5.11 (13-H), 4.43 (1′-H), 4.25 (11-H), 3.70 (3-H), 3.72 (9-$H_a$), 3.55 (5′-H), 3.49 (5-H), 3.48 (10-H), 3.25 (2′-H), 2.58 (2-H), 2.53 (8-H), 2.51 (3′-H), 2.37 (9-$H_b$), 2.25 (3′-$N(CH_3)_2$), 2.15 (4-H), 1.88 (14-$H_a$), 1.47 (7-$H_a$), 1.65 (4′-$H_a$), 1.52 (14-$H_b$), 1.32 (2-$CH_3$), 1.27 (6-$CH_3$), 1.25 (5′-$CH_3$), 1.24 (4′-$H_b$), 1.23 (10-$CH_3$), 1.20 (12-$CH_3$), 1.14 (7-$H_b$), 1.02 (4-$CH_3$), 1.00 (8-$CH_3$), 0.90 (15-H). $^{13}$C NMR (125 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 141.9 (C), 128.1 (2 × CH), 127.8 (2 × CH),126.2 (CH), 49.6 ($CH_2$); *macrolide*: 174.5 (C-1), 153.8 (C=N), 106.5 (C-1′), 93.8 (C-5), 80.2 (C-11), 78.5 (C-3), 75.5 (C-6), 75.5 (C-13), 71.9 (C-12), 70.4 (C-2′), 70.2 (C-5′), 65.6 (C-3′), 59.6 (C-10), 50.5 (C-9), 44.7 (C-2), 36.7 (4-C), 36.5 (C-7), 40.3 (3′-$N(CH_3)_2$), 28.0 (C-4′), 25.8 (6-$CH_3$), 24.7 (8-C), 20.7 (8-$CH_3$), 20.7 (C-14), 21.2 (5′-$CH_3$), 16.1 (2-$CH_3$), 10.5 (C-15), 15.4 (12-$CH_3$), 14.1 (10-$CH_3$), 7.8 (4-$CH_3$). HRMS (ES) calcd for $C_{45}$ $H_{75}N_3O_{12}$ ($M+H^+$) 692.4481, found 692.4484.

### 4.15. 9a,11-*O*-(*N*′-Benzylcarbonimidoyl)-3-decladinosyl-6-*O*-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (24)

According to the general procedure 270 mg of **20** (0.36 mmol) afforded **24** (64 mg, 25%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3571, 3434, 2972, 2937, 2877, 2834, 2787, 1737, 1688, 1495, 1457, 1410, 1379, 1352, 1294, 1212, 1162, 1115, 1076, 1050, 1002, 966, 939, 891, 835, 733, 699. $^1$H NMR (500 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 7.28 (2 × CH), 7.38 (2 × CH), 7.17 (CH), 4.51 ($CH_2$); *macrolide*: 5.08 (13-H), 4.43 (1′-H), 4.21 (11-H), 3.73 (5-H), 3.65 (3-H), 3.63 (9-$H_a$), 3.44 (10-H), 3.54 (5′-H), 3.24 (2′-H), 3.03 (6-$OCH_3$), 2.60 (2-H), 3.46 (3′-H), 2.27 (9-$H_b$), 2.58 (8-H), 2.33 (4-H), 2.24 (3′-$N(CH_3)_2$), 1.88 (14-$H_a$), 1.64 (4′-$H_a$), 1.50 (14-$H_b$), 1.38 (7-$H_a$), 1.32 (2-$CH_3$), 1.31 (6-$CH_3$), 1.25 (4′-$H_b$), 1.25 (5′-$CH_3$), 1.21 (12-$CH_3$), 1.21 (7-$H_b$), 1.18(10-$CH_3$), 0.94 (8-$CH_3$), 1.04 (4-$CH_3$), 0.88(15-H). $^{13}$C NMR (125 MHz, $CDCl_3$) [$\delta$/ppm] *benzyl*: 142.8 (C), 127.4 (2 × CH), 126.8 (2 × CH), 125.4 (CH), 49.6 ($CH_2$); *macrolide*: 174.0(C-1), 152.4 (C=N), 106.2 (C-1′), 88.9 (C-5), 78.6 (C-11), 78.6 (C-3), 77.8 (C-6), 75.2 (C-13), 71.2 (C-12), 70.0 (C-2′), 65.9 (C-5′), 65.2 (C-3′), 58.9 (C-10), 50.0 (C-9), 49.3 (6-$OCH_3$), 44.2 (C-2), 34.7 (4-C), 36.2 (C-7), 39.6 (3′-$N(CH_3)_2$), 27.4 (C-4′), 23.9 (8-C), 20.7 (5′-$CH_3$), 19.8 (8-$CH_3$), 18.5 (6-$CH_3$), 20.2 (C-14), 15.3 (2-$CH_3$), 13.6 (10-$CH_3$), 14.8 (12-$CH_3$), 9.8 (C-15), 7.1 (4-$CH_3$). HRMS (ES) calcd for $C_{45}$ $H_{75}N_3O_{12}$ ($M+H^+$) 706.4637, found 706.4638.

### 4.16. One-pot synthesis of 25–33 using polymer supported Mukaiyama reagent (P-Mukaiyama)

*General procedure*: To a solution of **1**–**4** in acetonitrile (*c* 0.03 g/ml), triethylamine (3 equiv), the corresponding isothiocyanate (3 equiv), and P-Mukaiyama reagent (1.18 mol/g, 1.5 equiv) were added and the reaction mixture shaken at 60 °C overnight. The reaction mixture was cooled to room temperature and the P-Mukaiyama reagent separated by filtration. After evaporation of the solvent, the crude product was purified on the Flashmaster personal—solid phase extraction techniques (SPE 10 g). Solvent system gradient (98–93% $CH_2Cl_2$/($CH_3OH$/$NH_4OH$ = 9:1.5)) and 10 ml/min flow rate was used. Combining and evaporating the chromatographically homogenous fractions gave the final products **25**–**33**.

### 4.17. 9a,11-*O*-(*N*′-Isopropropylcarbonimidoyl)-9-deoxo-9a-aza-9a-homoerythromycin A (25)

According to the general procedure, reaction of 300 mg of **1** (0.41 mmol) and *i*-propyl isothiocyanate afforded **25** (130 mg, 39%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3451, 2971, 2935, 1740, 1688, 1524, 1461, 1379, 1255, 1165, 1111, 1079, 1053, 1002, 953, 894, 863, 835, 799, 727, 681, 639. $^1$H NMR (500 MHz, $CDCl_3$) [$\delta$/ppm] *isopropyl*: 3.91 (CH), 1.25 (2 × $CH_3$); *macrolide*: 5.07 (13-H), 4.93 (1″-H), 4.40 (1′-H), 4.23 (11-H), 4.05 (3-H), 4.04 (5″-H), 3.85 (9-$H_a$), 3.63 (5-H), 3.57 (10-H), 3.49 (5′-H), 3.30 (3″-$OCH_3$), 3.21 (2′-H), 3.03 (4″-H), 2.93 (2-H), 2.48 (9-$H_b$), 2.42 (3′-H), 2.40 (8-H), 2.37 (2″-$H_a$), 2.28 (3′-$N(CH_3)_2$), 1.97 (4-H), 1.92 (14-$H_a$), 1.67 (4′-$H_a$), 1.55 (7-$H_a$), 1.53 (14-$H_b$), 1.52 (2″-$H_b$), 1.38 (6-$CH_3$), 1.32 (5″-$CH_3$), 1.26 (7-$H_b$), 1.25 (4′-$H_b$), 1.25 (2-$CH_3$), 1.25 (3″-$CH_3$), 1.21 (5′-$CH_3$), 1.21 (10-$CH_3$), 1.17 (12-$CH_3$), 1.07 (4-$CH_3$), 1.02 (8-$CH_3$), 0.89 (15-H). $^{13}$C NMR (125 MHz, $CDCl_3$) [$\delta$/ppm] *isopropyl*: 46.9 (CH), 23.9 (2 × $CH_3$); *macrolide*: 174.2(C-1), 153.2 (C=N), 103.0 (C-1′), 96.7 (C-1″), 93.9 (C-5), 80.7 (C-11), 80.7 (C-3), 75.4 (C-6), 77.8 (C-4″), 75.7 (C-13), 72.5 (C-3″), 71.7 (C-12), 70.9 (C-2′), 68.7 (C-5′), 65.6 (C-5″), 65.4 (C-3′), 59.5 (C-10), 50.2 (C-9), 49.2 (3″-$OCH_3$), 44.7 (C-2), 38.8 (4-C), 36.4 (C-7), 40.2 (3′-$N(CH_3)_2$), 35.2 (2″-C), 28.5 (C-4′), 27.2 (6-$CH_3$), 24.3 (8-C), 21.3 (3″-$CH_3$), 20.7 (8-$CH_3$), 20.3 (C-14), 21.3 (5′-$CH_3$), 18.5 (5″-$CH_3$), 16.7 (2-$CH_3$), 15.4 (12-$CH_3$), 13.7 (10-$CH_3$), 10.2 (C-15), 9.2 (4-$CH_3$). HRMS (ES) calcd for $C_{41}$ $H_{75}N_3O_{12}$ ($M+H^+$) 802.5424, found 802.5426.

### 4.18. 9a,11-*O*-(*N*′-Isopropropylcarbonimidoyl)-6-*O*-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (26)

According to the general procedure, reaction of 300 mg of **2** (0.40 mmol) and *i*-propyl isothiocyanate afforded **26** (112 mg, 40%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3565, 3429, 2973, 2833, 2785, 1737, 1708, 1463, 1456, 1402, 1378, 1337, 1293, 1268, 1246, 1164, 1112, 1054, 1012, 998, 951, 939, 916, 891, 864, 837, 796, 755, 713, 676, 640. $^1$H NMR (500 MHz, $CDCl_3$) [$\delta$/ppm] *isopropyl*: 3.79 (CH), 1.21 (2 × $CH_3$); *macrolide*: 5.10 (13-H), 4.95 (1″-H), 4.48 (1′-H), 4.08 (5″-H), 4.03 (11-H), 3.85 (3-H), 3.40 (9-$H_a$), 3.80 (5-H), 3.52 (5′-H), 3.37 (10-H), 3.32 (3″-$OCH_3$), 3.23 (6-$OCH_3$), 3.20 (2′-H), 3.04 (4″-H), 2.95 (2-H), 2.44 (3′-H), 2.42 (8-H), 2.35 (2″-$H_a$), 2.29 (3′-$N(CH_3)_2$), 2.19 (9-$H_b$), 2.10 (4-H), 1.94 (14-$H_a$), 1.64 (4′-$H_a$), 1.60 (2″-$H_b$), 1.53 (14-$H_b$), 1.34 (6-$CH_3$), 1.32 (5″-$CH_3$), 1.31 (7-$H_a$), 1.29 (7-$H_b$), 1.26 (2-$CH_3$), 1.23(3″-$CH_3$), 1.22 (4′-$H_b$), 1.22 (5′-$CH_3$), 1.17 (12-$CH_3$), 1.14 (10-$CH_3$), 1.06 (4-$CH_3$), 0.91 (8-$CH_3$), 0.90 (15-H). $^{13}$C NMR (125 MHz, $CDCl_3$) [$\delta$/ppm] *isopropyl*: 46.6 (*i*-Pr-CH), 24.9 (2 × $CH_3$); *macrolide*: 174.0 (C-1), 149.0 (C=N), 102.1 (C-1′), 96.6 (C-1″), 80.6 (C-5), 79.6 (C-3), 78.4 (C-11), 78.4 (C-6), 77.8 (C-4″), 75.9 (C-13), 72.7 (C-3″), 71.8 (C-12), 71.0 (C-2′), 68.4 (C-5′), 65.8 (C-5″), 65.5 (C-3′), 57.8 (C-10), 50.2 (C-9), 49.2 (3″-$OCH_3$), 44.8 (C-2), 40.2 (3′-$N(CH_3)_2$), 37.8 (4-C), 36.1 (C-7), 35.2 (2″-C), 28.5 (C-4′), 24.5 (8-C), 21.4 (5′-$CH_3$), 21.4 (3″-$CH_3$), 20.8 (5″-$CH_3$), 20.5 (8-$CH_3$), 20.4 (C-14), 18.6 (6-$CH_3$), 16.9 (2-$CH_3$), 15.1 (12-$CH_3$), 13.8 (10-$CH_3$), 10.3 (C-15), 9.4 (4-$CH_3$). HRMS (ES) calc. for $C_{42}H_{77}N_3O_{12}$: 816.5586 ($M+H^+$), found: 816.5602.

### 4.19. 9a,11-*O*-(*N*′-Isopropylcarbonimidoyl)-3-decladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A (27)

According to the general procedure, reaction of 300 mg of **3** (0.52 mmol) and *i*-propyl isothiocyanate afforded **27** (64 mg, 19%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3447, 2971, 2936, 2877, 2788, 1738, 1686, 1459, 1408, 1379, 1255, 1215, 1163, 1113, 1075, 1048, 1002, 949, 894, 836, 726, 684. $^1$H NMR (500 MHz, $CDCl_3$) [$\delta$/ppm] *isopropyl*: 3.98 (CH), 1.29 (2 × $CH_3$); *macrolide*: 5.15 (13-H), 4.44 (1′-H), 4.30 (11-H), 4.06 (9-$H_a$), 3.71 (3-H), 3.55 (5′-H), 3.58 (10-H), 3.51 (5-H), 3.25 (2′-H), 2.58 (2-H), 2.58 (8-H), 2.50 (3′-H), 2.43 (9-$H_b$), 2.25 (3′-$N(CH_3)_2$), 2.08 (4-H), 1.94 (14-$H_a$), 1.42 (7-$H_a$), 1.66 (4′-$H_a$), 1.56 (14-$H_b$), 1.36 (6-$CH_3$), 1.32 (2-$CH_3$), 1.28 (5′-$CH_3$), 1.27 (4′-$H_b$), 1.32 (10-$CH_3$), 1.27 (12-$CH_3$), 1.17 (7-H$_b$), 1.01 (4-CH$_3$), 1.05 (8-CH$_3$), 0.91 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [δ/ppm] *isopropyl*: 47.5 (CH), 23.6 (2 × CH$_3$); *macrolide*: 174.7 (C-1), 154.0 (C=N), 106.4 (C-1′), 93.8 (C-5), 81.5 (C-11), 78.2 (C-3), 75.3 (C-13), 74.5 (C-6), 71.8 (C-12), 70.3 (C-2′), 70.2 (C-5′), 65.5 (C-3′), 60.3 (C-10), 50.6 (C-9), 44.7 (C-2), 36.8 (4-C), 36.1 (C-7), 40.2 (3′-N(CH$_3$)$_2$), 27.9 (C-4′), 25.9 (6-CH$_3$), 24.5 (8-C), 20.6 (8-CH$_3$), 20.5 (C-14), 21.1 (5′-CH$_3$), 16.0 (2-CH$_3$), 10.2 (C-15), 15.8 (12-CH$_3$), 19.3 (10-CH$_3$), 7.7 (4-CH$_3$). HRMS (ES) calcd for $C_{33}H_{61}N_3O_9$ (M+H$^+$) 644.4481, found 644.4455.

### 4.20. 9a,11-*O*-[*N*′-(1-Naphtyl)carbonimidoyl]-9-deoxo-9a-aza-9a-homoerythromycin A (28)

According to the general procedure, reaction of 300 mg of **1** (0.41 mmol) and 1-naphtyl isothiocyanate afforded **28** (67 mg, 18%) as a white foam. IR (KBr) [ν/cm$^{-1}$]: 3571, 3452, 2970, 2931, 1739, 1674, 1573, 1505, 1461, 1388, 1253, 1165, 1111, 1052, 1001, 961, 895, 796, 721, 672. $^1$H NMR (500 MHz, CDCl$_3$) [δ/ppm] *naphtyl*: 8.37 (CH), 7.76 (CH), 7.46 (2 × CH), 7.43 (2 × CH), 7.40 (CH); *macrolide*: 5.00 (13-H), 4.96 (1″-H), 4.45 (1′-H), 4.33 (11-H), 4.20 (3-H), 4.06 (5″-H), 3.72 (9-H$_a$), 3.68 (5-H), 3.59 (10-H), 3.51 (5′-H), 3.31 (3″-OCH$_3$), 3.26 (2′-H), 3.00 (4″-H), 2.95 (2-H), 2.51 (8-H), 2.48 (3′-H), 2.48 (9-H$_b$), 2.36 (2″-H$_a$), 2.34 (3′-N(CH$_3$)$_2$), 2.17 (4-H), 1.79 (14-H$_a$), 1.69 (4′-H$_a$), 1.57 (7-H$_a$), 1.60 (2″-H$_b$), 1.47 (14-H$_b$), 1.44 (7-H$_b$), 1.35 (6-CH$_3$), 1.28 (5″-CH$_3$), 1.28 (2-CH$_3$), 1.26 (4′-H$_b$), 11.24 (10-CH$_3$), 1.23 (3″-CH$_3$), 1.23 (5′-CH$_3$), 1.16 (12-CH$_3$), 1.13 (4-CH$_3$), 1.02 (8-CH$_3$), 0.82 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [δ/ppm] *naphtyl*: 143.9 (C), 134.2 (C), 129.6 (C), 127.5 (CH), 126.8 (CH), 125.2 (CH), 124.4 (2 × CH), 121.2 (CH), 118.5 (CH); *macrolide*: 174.1 (C-1), 150.0 (C=N), 103.0 (C-1′), 96.7 (C-1″), 84.3 (C-5), 80.8 (C-3), 80.0 (C-11), 77.9 (C-4″), 75.7 (C-13), 75.3 (C-6), 72.7 (C-3″), 71.9 (C-12), 71.1 (C-2′), 68.7 (C-5′), 65.8 (C-5″), 65.7 (C-3′), 58.1 (C-10), 50.4 (C-9), 49.4 (3″-OCH$_3$), 44.8 (C-2), 40.4 (3′-N(CH$_3$)$_2$), 38.8 (4-C), 36.8 (C-7), 35.3 (2″-C), 28.9 (C-4′), 27.4 (6-CH$_3$), 25.3 (8-C), 21.5 (3″-CH$_3$), 21.0 (8-CH$_3$), 20.4 (C-14), 21.4 (5′-CH$_3$), 18.7 (5″-CH$_3$), 16.8 (2-CH$_3$), 15.2 (12-CH$_3$), 13.6 (10-CH$_3$), 9.5 (4-CH$_3$), 10.4 (C-15). HRMS (ES) calcd for $C_{45}H_{75}N_3O_{12}$ (M+H$^+$) 886.5424, found 886.5388.

### 4.21. 9a,11-*O*-[*N*′-(1-Naphtyl)carbonimidoyl]-3-decladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A (29)

According to the general procedure, reaction of 300 mg of **3** (0.52 mmol) and 1-naphtyl isothiocyanate afforded **29** (193 mg, 51%) as a white solid. IR (KBr) [ν/cm$^{-1}$]: 3451, 2936, 1738, 1674, 1573, 1505, 1458, 1388, 1300, 1253, 1215, 1163, 1112, 1073, 1047, 980, 945, 894, 796, 777, 723, 673. $^1$H NMR (500 MHz, CDCl$_3$) [δ/ppm] *naphtyl*: 8.33 (CH), 7.75 (CH), 7.48 (2 × CH), 7.41 (CH), 7.48 (2 × CH); *macrolide*: 5.06 (13-H), 4.45 (1′-H), 4.35 (11-H), 3.82 (3-H), 3.77 (9-H$_a$), 3.60 (5-H), 3.53 (5′-H), 3.51 (10-H), 3.28 (2′-H), 2.62 (2-H), 2.59 (8-H), 2.52 (3′-H), 2.45 (9-H$_b$), 2.28 (3′-N(CH$_3$)$_2$), 2.38 (4-H), 1.80 (14-H$_a$), 1.68 (7-H$_a$), 1.66 (4′-H$_a$), 1.48 (14-H$_b$), 1.36 (2-CH$_3$), 1.27 (7-H$_b$), 1.27 (10-CH$_3$), 1.26 (4′-H$_b$), 1.26 (6-CH$_3$), 1.23 (5′-CH$_3$), 1.20 (12-CH$_3$), 1.08 (4-CH$_3$), 1.04 (8-CH$_3$), 0.84 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [δ/ppm] *naphtyl*: 143.6 (C), 134.2 (C), 129.7 (C), 127.5 (CH), 126.8 (CH), 125.3 (CH), 124.3 (2 × CH), 121.4 (CH), 118.5 (CH); *macrolide*: 174.5(C-1), 150.2 (C=N), 106.5 (C-1′), 93.7 (C-5), 80.0 (C-11), 78.5 (C-3), 74.6 (C-6), 75.4 (C-13), 71.9 (C-12), 70.4 (C-2′), 70.1 (C-5′), 65.7 (C-3′), 58.5 (C-10), 50.6 (C-9), 44.7 (C-2), 36.8 (4-C), 36.9 (C-7), 40.2 (3′-N(CH$_3$)$_2$), 28.2 (C-4′), 26.1 (6-CH$_3$), 25.2 (8-C), 20.7 (8-CH$_3$), 20.5 (C-14), 21.2 (5′-CH$_3$), 16.1 (2-CH$_3$), 15.3 (12-CH$_3$), 13.6 (10-CH$_3$), 10.4 (C-15), 7.8 (4-CH$_3$). HRMS (ES) calcd for $C_{45}H_{75}N_3O_{12}$ (M+H$^+$) 728.4481, found 728.4471.

### 4.22. 9a,11-*O*-[*N*′-(1-Naphtyl)carbonimidoyl]-6-*O*-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (30)

According to the general procedure, reaction of 300 mg of **2** (0.40 mmol) and 1-naphtyl isothiocyanate afforded **30** (163 mg, 44%) as a white foam. IR (KBr) [ν/cm$^{-1}$]: 3451, 2972, 2937, 2831, 2786, 1738, 1675, 1573, 1505, 1461, 1387, 1252, 1164, 1112, 1053, 1001, 941, 891, 834, 795, 777, 719, 673, 639. $^1$H NMR (500 MHz, CDCl$_3$) [δ/ppm] *naphtyl*: 8.38 (CH), 7.53 (CH), 7.44 (CH), 7.44 (2 × CH), 7.39 (2 × CH); *macrolide*: 5.02 (13-H), 4.98 (1″-H), 4.51 (1′-H), 4.25 (11-H), 4.07 (5″-H), 3.95 (5-H), 3.84 (3-H), 3.68 (9-H$_a$), 3.54 (10-H), 3.52 (5′-H), 3.32 (3″-OCH$_3$), 3.22 (6-OCH$_3$), 3.22 (2′-H), 3.03 (4″-H), 2.98 (2-H), 2.57 (8-H), 2.45 (3′-H), 2.39 (9-H$_b$), 2.35 (2″-H$_a$), 2.00 (3′-N(CH$_3$)$_2$), 2.22 (4-H), 1.81 (14-H$_a$), 1.67 (4′-H$_a$), 2.31 (7-H$_a$), 1.62 (2″-H$_b$), 1.47 (14-H$_b$), 1.42 (7-H$_b$), 1.33 (6-CH$_3$), 1.29 (5″-CH$_3$), 1.31 (2-CH$_3$), 1.26 (4′-H$_b$), 1.26 (3″-CH$_3$), 1.22 (10-CH$_3$), 1.21 (5′-CH$_3$), 1.17 (12-CH$_3$), 1.10 (4-CH$_3$), 0.97 (8-CH$_3$), 0.82 (15-H). $^{13}$C NMR (125 MHz, DMSO) [δ/ppm] *naphtyl*: 144.4 (C), 134.2 (C), 129.7 (C), 127.4 (CH), 126.5 (CH), 125.2 (CH), 124.7 (CH), 124.3 (CH), 120.9 (CH), 118.5 (CH); *macrolide*: 174.1 (C-1), 149.8 (C=N), 102.3 (C-1′), 96.7 (C-1″), 80.0 (C-3), 79.7 (C-5), 79.8 (C-11), 78.7 (C-6), 77.9 (C-4″), 75.8 (C-13), 72.9 (C-3″), 71.9 (C-12), 71.2 (C-2′), 68.5 (C-5′), 66.2 (C-5″), 65.6 (C-3′), 58.0 (C-10), 51.7 (6-OCH$_3$), 50.6 (C-9), 49.4 (3″-OCH$_3$), 44.8 (C-2), 40.4 (3′-N(CH$_3$)$_2$), 38.0 (4-C), 36.5 (C-7), 35.7 (2″-C), 28.8 (C-4′), 25.5 (8-C), 21.5 (5′-CH$_3$), 20.8 (3″-CH$_3$), 20.7 (8-CH$_3$), 20.4 (C-14), 20.8 (6-CH$_3$), 18.7 (5″-CH$_3$), 17.0 (2-CH$_3$), 15.3 (12-CH$_3$), 13.7 (10-CH$_3$), 9.6 (4-CH$_3$), 10.4 (C-15). HRMS (ES) calcd for $C_{49}H_{77}N_3O_{12}$ (M+H$^+$) 900.5586, found 900.5147

### 4.23. 9a,11-*O*-[*N*′-(1-Naphtyl)carbonimidoyl]-3-decladinosyl-6-O-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (31)

According to the general procedure, reaction of 300 mg of **4** (0.51 mmol) and 1-naphtyl isothiocyanate afforded **31** (67 mg, 17%) as a white foam. IR (KBr) [ν/cm$^{-1}$]: 3442, 3044, 2972, 2936, 2877, 2832, 2787, 1736, 1674, 1572, 1505, 1459, 1388, 1298, 1252, 1213, 1162, 1114, 1077, 1050, 980, 940, 891, 796, 777, 724, 672. $^1$H NMR (500 MHz, CDCl$_3$) [δ/ppm] *naphtyl*: 8.41 (CH), 7.49 (CH), 7.45 (CH), 7.45 (2 × CH), 7.39 (2 × CH); *macrolide*: 5.09 (13-H), 4.49 (1′-H), 4.33 (11-H), 3.77 (5-H), 3.72 (9-H$_a$), 3.68 (3-H), 3.51 (5′-H), 3.49 (10-H), 3.26 (2′-H), 3.00 (6-OCH$_3$), 2.67 (8-H), 2.63 (2-H), 2.47 (3′-H), 2.45 (4-H), 2.37 (9-H$_b$), 2.25 (3′-N(CH$_3$)$_2$), 1.84 (14-H$_a$), 1.64 (4′-H$_a$), 1.55 (7-H$_a$), 1.49 (14-H$_b$), 1.35 (2-CH$_3$), 1.28 (6-CH$_3$), 1.25 (4′-H$_b$), 1.23 (7-H$_b$), 1.28 (10-CH$_3$), 1.24 (12-CH$_3$), 1.23 (5′-CH$_3$), 1.08 (4-CH$_3$), 0.97 (8-CH$_3$), 0.84 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [δ/ppm] *naphtyl*: 144.5 (C), 134.7 (C), 130.2 (C), 127.8 (CH), 126.7 (CH), 125.6 (CH), 125.1 (CH), 124.7 (CH), 121.3 (CH), 118.6 (CH); *macrolide*: 174.9 (C-1), 149.7 (C=N), 107.3 (C-1′), 89.7 (C-5), 79.9 (C-11), 79.4 (C-3), 78.7 (C-6), 76.1 (C-13), 72.2 (C-12), 71.0 (C-5′), 70.5 (C-2′), 66.2 (C-3′), 58.8 (C-10), 51.1 (C-9), 50.7 (6-OCH$_3$), 45.2 (C-2), 40.6 (3′-N(CH$_3$)$_2$), 37.0 (C-7), 35.9 (4-C), 28.9 (C-4′), 25.4 (8-C), 21.6 (5′-CH$_3$), 21.0 (C-14), 20.8 (8-CH$_3$), 19.9 (6-CH$_3$), 16.4 (2-CH$_3$), 15.9 (12-CH$_3$), 14.2 (10-CH$_3$), 10.7 (C-15), 8.3 (4-CH$_3$). HRMS (ES) calcd for $C_{41}H_{63}N_3O_9$ (M+H$^+$) 742.4643, found 742.4650.

### 4.24. 9a,11-*O*-{*N*′-[4-(3-Methoxy)biphenyl]carbonimidoyl}-9-deoxo-9a-aza-9a-homoerythromycin A (32)

According to the general procedure, reaction of 250 mg of **1** (0.34 mmol) and 3-(2-methoxy)biphenyl isothiocyanate afforded **32** (130 mg, 41%) as a white foam. IR (KBr) [ν/cm$^{-1}$]: 3508, 3466, 2971, 2936, 1741, 1688, 1579, 1545, 1512, 1489, 1461, 1378, 1246, 1165, 1111, 1053, 1010, 951, 834, 806, 762, 699. $^1$H NMR (500 MHz, CDCl$_3$) [δ/ppm] *2-methoxybiphenyl*: 7.65 (2 × CH), 7.38

(CH), 7.35 (2 × CH), 7.24 (CH), 7.20 (CH), 6.92 (CH), 3.87 (OCH$_3$); *macrolide*: 4.90 (13-H), 4.90 (1″-H), 4.41 (1′-H), 4.31 (11-H), 4.25 (3-H), 4.07 (5″-H), 3.68 (5-H), 3.58 (9-H$_a$), 3.57 (10-H), 3.51 (5′-H), 3.30 (3″-OCH$_3$), 3.27 (2′-H), 3.03 (4″-H), 2.87 (2-H), 2.54 (3′-H), 2.45 (8-H), 2.43 (9-H$_b$), 2.36 (3′-N(CH$_3$)$_2$), 2.35 (2″-H$_a$), 2.06 (4-H), 1.81 (14-H$_a$), 1.74 (4′-H$_a$), 1.59 (2″-H$_b$), 1.51 (7-H$_a$), 1.46 (14-H$_b$), 1.42 (7-H$_b$), 1.40 (6-CH$_3$), 1.31 (5″-CH$_3$), 1.27 (4′-H$_b$), 1.25 (3″-CH$_3$), 1.23 (5′-CH$_3$), 1.21 (2-CH$_3$), 1.24 (10-CH$_3$), 1.15 (12-CH$_3$), 1.08 (4-CH$_3$), 0.99 (8-CH$_3$), 0.78 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [$\delta$/ppm] *2-methoxybiphenyl*: 150.0 (C), 141.2 (C), 137.2 (C), 133.3 (C), 128.3 (2 × CH),126.8 (2 × CH), 126.1 (CH), 123.0 (CH), 121.1 (CH), 111.1 (CH), 55.8 (OCH$_3$); *macrolide*: 174.0 (C-1), 151.7 (C=N), 103.4 (C-1′), 96.7 (C-1″), 84.6 (C-5), 80.7 (C-3), 79.9 (C-11), 77.9 (C-4″), 75.8 (C-13), 74.5 (C-6), 72.6 (C-3″), 71.7 (C-12), 70.9 (C-2′), 68.7 (C-5′), 65.6 (C-3′), 65.4 (C-5″), 58.4 (C-10), 50.3 (C-9), 50.4 (3″-OCH$_3$), 44.7 (C-2), 40.3 (3′-N(CH$_3$)$_2$), 37.9 (4-C), 37.9 (C-7), 35.1 (2″-C), 29.2 (C-4′), 27.1 (6-CH$_3$), 21.4 (3″-CH$_3$), 21.2 (5′-CH$_3$), 20.9 (8-C), 20.9 (8-CH$_3$), 20.3 (C-14), 18.4(5″-CH$_3$), 16.5 (2-CH$_3$), 15.2 (12-CH$_3$), 13.7 (10-CH$_3$), 10.2 (C-15), 9.4 (4-CH$_3$). HRMS (ES) calcd for $C_{51}$ $H_{79}N_3O_{13}$ (M+H$^+$) 942.5685, found 942.5677.

### 4.25. 9a,11-*O*-{*N*′-[4-(3-Methoxy)biphenyl]carbonimidoyl}-3-decladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A (33)

According to the general procedure, reaction of 300 mg of **3** (0.52 mmol) and 3-(2-methoxy)biphenyl isothiocyanate afforded **33** (216 mg, 53%) as a white foam. IR (KBr) [$\nu$/cm$^{-1}$]: 3450, 2971, 2936, 2878, 2786, 1738, 1687, 1675, 1597, 1545, 1512, 1489, 1461, 1379, 1296, 1246, 1208, 1163, 1113, 1073, 1050, 995, 946, 889, 762, 699. $^1$H NMR (500 MHz, CDCl$_3$) [$\delta$/ppm] *2-methoxybiphenyl*: 7.69 (2 × CH), 7.36 (2 × CH),7.41 (CH), 7.24 (CH), 7.20 (CH), 6.90 (CH), 3.84 (OCH$_3$); *macrolide*: 5.02 (13-H), 4.40 (1′-H), 4.28 (11-H), 3.69 (9-H$_a$), 3.76 (3-H), 3.47 (5′-H), 3.48 (10-H), 3.55 (5-H), 3.26 (2′-H), 2.58 (2-H), 2.57 (8-H), 2.49 (3′-H), 2.39 (9-H$_b$), 2.25 (3′-N(CH$_3$)$_2$), 2.25 (4-H), 1.83 (14-H$_a$), 1.61 (7-H$_a$), 1.61 (4′-H$_a$), 1.48 (14-H$_b$), 1.32 (6-CH$_3$), 1.31 (2-CH$_3$), 1.21 (5′-CH$_3$), 1.23 (4′-H$_b$), 1.29 (10-CH$_3$), 1.22 (12-CH$_3$), 1.22 (7-H$_b$), 1.03 (4-CH$_3$), 1.02 (8-CH$_3$), 0.81 (15-H). $^{13}$C NMR (125 MHz, CDCl$_3$) [$\delta$/ppm] *2-methoxybiphenyl*: 149.8 (C), 141.1 (C), 136.8 (C), 133.5 (C), 128.3 (2 × CH), 126.8 (2 × CH), 126.0 (CH), 123.0 (CH), 121.0 (CH), 111.3 (CH), 55.8 (OCH$_3$); *macrolide*: 174.3 (C-1), 151.7 (C=N), 106.2 (C-1′), 93.8 (C-5), 79.8 (C-11), 78.3 (C-3), 75.6 (C-13), 74.1 (C-6), 71.5 (C-12), 70.2 (C-2′), 69.8 (C-5′), 65.4 (C-3′), 59.0 (C-10), 50.5 (C-9), 44.4 (C-2), 36.6 (4-C), 37.1 (C-7), 40.0 (3′-N(CH$_3$)$_2$), 27.9 (C-4′), 25.7 (6-CH$_3$), 25.1 (8-C), 20.3 (8-CH$_3$), 20.4 (C-14), 20.9 (5′-CH$_3$), 15.9 (2-CH$_3$), 15.4 (12-CH$_3$), 13.7 (10-CH$_3$), 10.2 (C-15), 7.6 (4-CH$_3$). HRMS (ES) calcd for $C_{43}$ $H_{65}N_3O_{10}$ (M+H$^+$) 784.4742, found 784.4720.

### 4.26. X-ray analysis of 13

The crystals suitable for X-ray analysis were grown from the *n*-hexane/ethyl acetate (9:1) solution by slow evaporation at room temperature over one week. Diffracted intensities were collected on an Oxford Diffraction Xcalibur 3 CCD diffractometer using graphite-monochromated MoK$\alpha$ radiation at room temperature. The CRYSALIS[10] program package was used for data collection, cell refinement and data reduction. The structure was solved by direct methods (SHELXS[11]) and refined with SHELXL-97,[12] both programs operating under the WINGX[13] program package. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms, except those residing on O1 W, were assigned calculated positions and allowed to ride on their carrier atoms. The Fourier difference map revealed peaks that were hard to interpret (identified as solvent molecules). Despite the extensive use of various restraints, etc., attempts to resolve the disorder were unsuccessful. The electron contribution of the solvent molecules was therefore subtracted from the diffraction data using the PLATON/SQUEEZE[14] procedure. The solvent molecules were found to occupy 996 Å$^3$ or 20% of the unit cell. A summary of crystal data is presented in Table 2. The programs PLATON,[15] MERCURY,[16] and ORTEP[17] were used for analysis of the structure and drawings preparation. Crystallographic data for the structure **13** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 779231.

**Table 2**
Crystal data and structure refinements parameters for **13**

| | |
|---|---|
| Formula | $C_{38}H_{61}N_3O_9 \cdot H_2O$ |
| Data collection temperature (K) | 293(2) |
| $M_r$ | 721.91 |
| Habit and color | Prismatic, colorless |
| Crystal dimension (mm$^3$) | 0.74 × 0.34 × 0.14 |
| Crystal system, space group | Monoclinic, $C^2$ |
| Unit cell parameters | |
| $a$ (Å) | 22.4880(9) |
| $b$ (Å) | 14.6680(4) |
| $c$ (Å) | 14.9460(5) |
| $\alpha$ (°) | 90.00 |
| $\beta$ (°) | 103.693(3) |
| $\gamma$ (°) | 90.00 |
| $V$ (Å3) | 4 |
| $Z$ | 4789.9(3) |
| $D_c$ (g cm$^{-3}$) | 1.001 |
| $\mu$ (mm$^{-1}$) | 0.072 |
| $F$(0 0 0) | 1568 |
| Diffractometer | Oxford Diffraction Xcalibur 3 |
| Radiation, $\lambda$ (Å) | MoK$\alpha$ = 0.71073 |
| Monochromator | Graphite |
| $\theta$ range for data collection (°) | 3.96–25.00 |
| Limiting indices | $-26 \leqslant -h \leqslant 26$, $-17 \leqslant k \leqslant 17$,<br>$--17 \leqslant l \leqslant 17$ |
| Reflections collected | 21734 |
| Independent reflections | 4334 [$R_{\text{int}}$ = 0.0316] |
| Observed reflections[$I > 2\sigma(I)$] | 2653 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Parameters/restraints | 484/5 |
| Goodness of fit on $F^2$ | 0.958 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1$ = 0.0617, $wR_2$ = 0.0900 |
| $R$ indices (all data) | $R_1$ = 0.1657, $wR_2$ = 0.1863 |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.172 and −0.208 |
| Weighing scheme | $w = [\sigma 2(F_o^2) + (1322P)^2 + 0.0000P] - 1$<br>where $P = (F_o^2 + 2F_c^2)/3$ |

### 4.27. In vitro antimicrobial activity

The MIC values were determined for all new compounds on a panel of macrolide susceptible Gram-positive (*S. aureus, S. pneumoniae, S. pyogenes*) and Gram-negative (*H. influenzae, Moraxella catarrhalis*) bacterial strains. Activity against *S. cervisiae* was used as a test for toxicity towards eukaryote cells. MIC values were determined using a microdilution test in Mueller–Hinton media, with each test compound dissolved in DMF (5 mg/mL). The concentration of substances in media was from 64 to 0.125 μg/mL. After 24 h incubation at 37 °C, the optical density was determined by measuring the absorbance at 600 nm. The MIC value was calculated as the concentration at which inhibition of bacterial growth was 90%.

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