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Novel 9a-carbamoyl- and 9a-thiocarbamoyl-3-decladinosyl-6-hydroxy and 6-methoxy derivatives of 15-membered macrolides

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Abstract—An efficient method for the synthesis of diverse 9a-carbamoyl- and 9a-thiocarbamoyl-3-decladinosyl-6-hydroxy and 3-decladinosyl-6-methoxy derivatives of 15-membered azalides has been developed. These derivatives bear various alkyl and aryl groups attached to macrolide scaffold through urea or thiourea moieties at 9a position. Chemical transformations of hydroxy group at position C-3 afforded range of ketolides, anhydrolides, hemiketals, cyclic ethers, and acylides. It has been shown that 6-hydroxy and 6-methoxy derivatives undergo different chemical transformations under otherwise identical reaction conditions. Antimicrobial properties of prepared compounds were evaluated.

1. Introduction

Macrolide antibiotics have been used for treatment of bacterial infections for more than 50 years.[1] However, it seems that broad potential of macrolides has not been fully explored yet. Most recently antibacterial macrolides have attracted considerable attention for two main reasons: (a) as with other antibiotics, active use of macrolides resulted in development of macrolide resistance that fuels a search for novel types of macrolides having better antibacterial activity, pharmacokinetic properties, and safety profiles (b) macrolide derivatives, especially 14- and 15-membered classes, have also become interesting for treating important chronic diseases, that is, asthma, chronic sinusitis, diffuse panbronchiolitis, cystic fibrosis, etc.[2,3] Some antibacterial macrolides proved active in treatment of malaria[4] and cancer.[5] For these alternative applications antibacterial activity of macrolides is a considerable disadvantage. The fact that such complex molecules could be used for multiple medical indications renders every novel macrolide class potentially useful either as antibiotics or as agents against other biological targets. There is also an evidence that immunomodulatory and antibacterial activity of 14-membered macrolides can be separated through appropriate chemical derivatization.[6]

Azalides (**1**) are group of semisynthetic 15-membered macrolides having nitrogen incorporated into macrolactone ring. They are derived from erythromycin (**2**), 14-membered macrolactone fermentation product of *Streptomyces erythreus* (Fig. 1). Azithromycin[7] (**1**, R = CH_3) is superior to erythromycin in regard of having better antibacterial activity as well as excellent pharmacokinetic properties and safety profile. Although it is one of the most widely prescribed antibiotics, azithromycin also shows therapeutic use in some inflammatory diseases and is already part of the standard therapy for treating diffuse panbronchiolitis.[2]

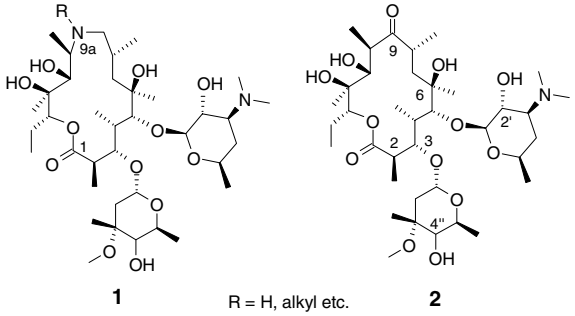

Figure 1. Chemical structures of azalides (**1**) and erythromycin A (**2**).

Keywords: Macrolide; Azalide; 3-Decladinosyl; Antibacterial activity.
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Due to their excellent properties and multiple medical use azalides are exquisite molecules for further chemical derivatization in order to prepare macrolides that can be screened against numerous biological targets of interest.

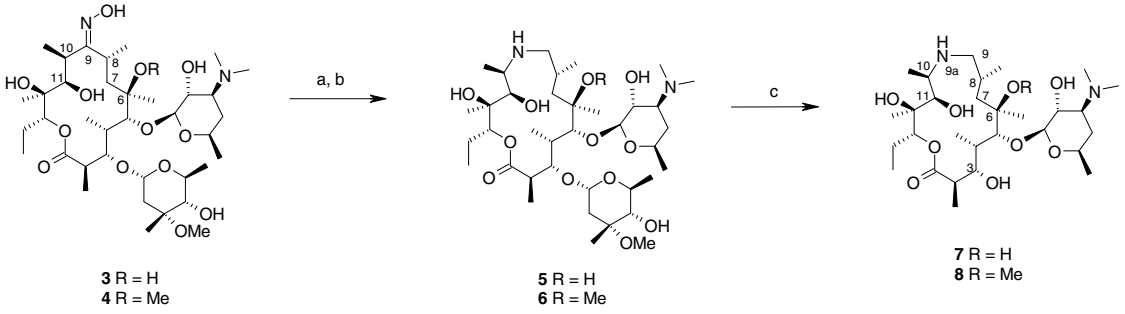
It is expected that introduction of unsaturated unit, that is, carbamoyl group, on nitrogen at position 9a of **1** (Fig. 1) will significantly change electronic properties and also steric environment in the 'upper part' of the macrolide. It will also serve as an excellent linker for the attachment of various groups affording preparation of a library of compounds. On the other hand, cleavage of cladinose unit can be achieved selectively and thus properties of the 'lower part' of 9a-carbamoyl 15-membered azalides substantially modified via further chemical modifications. While simple removal of cladinose sugar from macrolides significantly decreases antibacterial activity, some novel decladinosyl derivatives of 14-membered macrolides proved active against resistant bacterial strains.[8] We have undertaken synthetic study reported hereafter to investigate an efficient method for the preparation of various 3-decladinosyl derivatives of 9a-functionalized azalides. Antimicrobial properties of prepared compounds were also evaluated.

2. Results and discussion

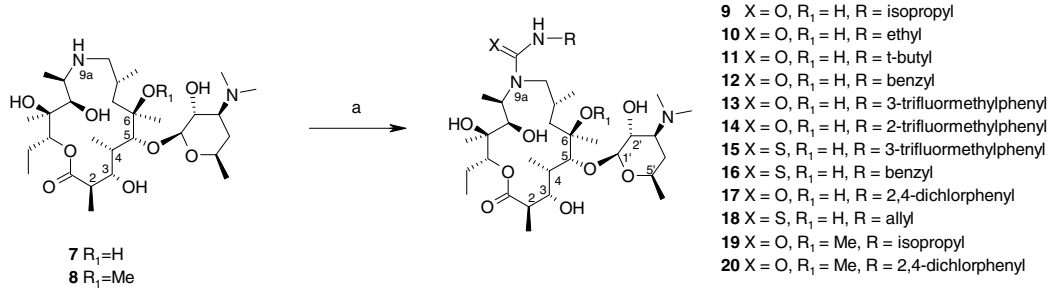
Synthetic study started with preparation of carbamoyl and thiocarbamoyl 3-decladinosyl derivatives of 6-hydroxy (6-OH) and 6-methoxy (6-OMe) azalides **7** and **8**, respectively. Well-known Beckmann rearrangement of erythromycin 9(*E*)-oxime **3** and hydrogenation of intermediary iminoether lead to azalide **5**.[7] As 6-OH group of azalides cannot be methylated,[10] 6-OMe derivative **6** was produced starting from clarithromycin 9(*E*)-oxime **4** by the same reaction sequence. Azalides **5** and **6** were treated with diluted acid to accomplish cleavage of cladinose producing compounds **7** and **8** (Scheme 1). Desosamine sugar remains intact under these conditions.

It has recently been shown that carbamoyl and thiocarbamoyl groups can be easily introduced at position 9a of **1** forming urea or thiourea moieties, respectively.[9] Thanks to the great number of commercially available isocyanates or isothiocyanates it is possible to attach various groups (alkyl, aryl, heteroaryl, etc.) through these linkages. As expected, high reactivity of secondary amino group in **7** and **8** toward isocyanates and isothiocyanates assured highly site-selective introduction of carbamoyl and thiocarbamoyl groups. A small library of 9a-carbamoyl and 9a-thiocarbamoyl 3-decladinosyl azalides was prepared according to Scheme 2.

IR spectra of prepared compounds **9**–**20** show new signals at 1618–1644 cm^{-1} and 1529–1596 cm^{-1} revealing the presence of carbamoyl and thiocarbamoyl groups, respectively. ^{1}H NMR data show new signal at 4.37–4.64 ppm that is attributed to carbamoyl NH (9a-NCXN′-H), while ^{13}C NMR show new singlets at 155.1–159.6 ppm for 9a-NCO or at 179.7–189.2 for 9a-NCS. Coupling constant H-2 to H-3 ($^{3}J_{2,3}$) of 10.4 Hz in **7** and 10.2 Hz in **8** (Table 1) defines the C-3 to C-5 'folded out' conformation of the macrocyclic ring.[11] Since the coupling constant $^{3}J_{2,3}$ of prepared derivatives **9**–**20** shows value of ~10 Hz, their conformation is also identified as 'folded out' indicating that the 'lower part'



Scheme 1. Reagents and condition: (a) TsCl, pyridine if R = Me or TsCl, $NaHCO_3$, acetone if R = H; (b) H_2-Pt/C, MeOH, 40 bar, 12 h; (c) water/HCl, pH 1.



Scheme 2. Reagents and conditions: (a) isocyanate or isothiocyanate, toluene, rt, 1 h.

Table 1. Key NMR data for 9a-carbamoyl and 9a-thiocarbamoyl 3-decladinosyl azalides

Compound	^{1}H	^{13}C (ppm)				
	$^3J_{2,3}$ (Hz)	C-6	C-3	C-1′	C-2′	C-5′
7	10.4	73.0	78.8	106.2	70.2	69.5
9–18	9.6–10.5	73.6–75.9	73.0–75.9	105.2–106.1	69.2–69.5	70.1–70.6
8	10.2	78.8	78.5	106.6	70.3	69.9
19	10.2	79.5	78.9	106.6	70.3	70.0
20	N.D.	79.1	79.7	106.9	70.5	69.9

of new macrolides is similar to parent compounds. Comparison of NMR data (Table 1) of 6-OH derivatives **9**–**18** to those of parent molecule **7** indicates substantial changes for signal C-3 (shifted upfield from 78.8 in **7** to ~74.5 ppm in **9**–**18**) and some changes for C-6 (shifted downfield from 73.0 in **7** to ~74.8 ppm in **9**–**18**). However, in the case of 6-OMe derivatives **19** and **20** no changes occurred for C-6 and C-3 in comparison to parent compound **8**. This shift of C-6 and C-3 in **9**–**18** can be attributed to free 6-OH group that may influence the orientation of desosamine sugar via hydrogen bonding as suggested by subtle changes in the shifts for C-1′, C-2′, and C-5′ in comparison to fixed positions of these signals in 6-OMe analogs.

In order to investigate modifications of the 'lower part' of macrolide via chemical transformations of hydroxyl group at C-3, two pairs of 9a-carbamoyl 6-OH (**9**, **17**) and 6-OMe azalides (**19**, **20**) were selected. They afforded formation of ketolides, anhydrolides, hemiketals, cyclic ethers, and acylides (Fig. 2). It was interesting to notice how 6-OH and 6-OMe derivatives undergo different transformations under otherwise identical reaction conditions, the later affording to our knowledge first 2,3-anhydrolides of 15-membered macrolides.

It was found that presence of urea and thiourea moiety does not influence the order of reactivity of the hydroxyl groups.[12] In order to perform chemical transformations on the hydroxyl group at position 3, 2′-hydroxyl group, which is the most reactive one, must be suitably protected. Hydroxyl groups at positions 6, 11, and 12 are much less reactive. Consequently, reaction of macrolides **9**, **17**, **19**, and **20** with acetic anhydride in the presence of a base smoothly afforded 2′-*O*-acetyl derivatives **21**, **22**, **23**, and **24**, respectively, that can be later easily deprotected by methanolysis.

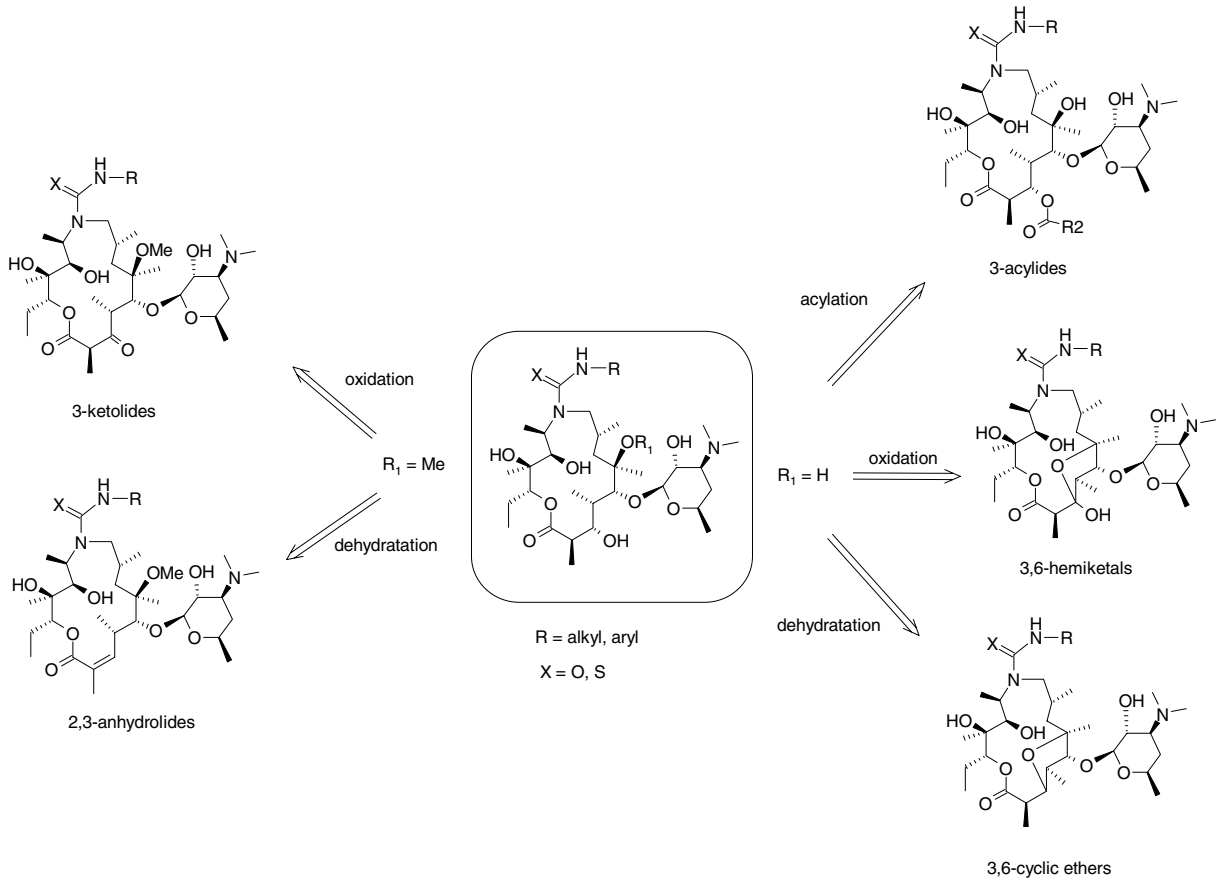
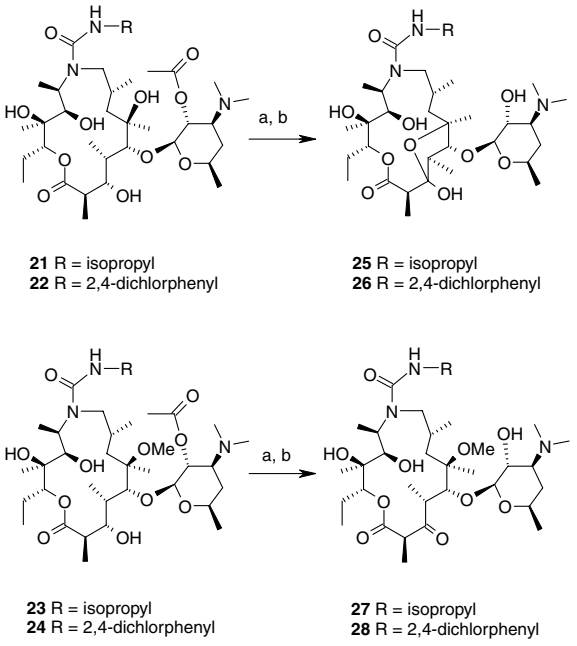


Figure 2. Modifications of the 'lower part' of 9a-carbamoyl and 9a-thiocarbamoyl azalides.

Whereas Pfitzner–Moffat oxidation[13] of 3-OH group of 3-decladinosyl-6-OH azalides **21** and **22** produces internal 3,6-hemiketal structures **25** and **26**, the same reaction conditions applied to 6-OMe derivatives **23** and **24** afford 3-keto derivatives **27** and **28** (Scheme 3). Formation of 3,6-hemiketals indicated that urea moiety at position 9a does not influence the proximity of 6-OH to C-3 required for the formation of 3,6-cyclic structures.[14]



21 R = isopropyl
22 R = 2,4-dichlorphenyl

25 R = isopropyl
26 R = 2,4-dichlorphenyl

23 R = isopropyl
24 R = 2,4-dichlorphenyl

27 R = isopropyl
28 R = 2,4-dichlorphenyl

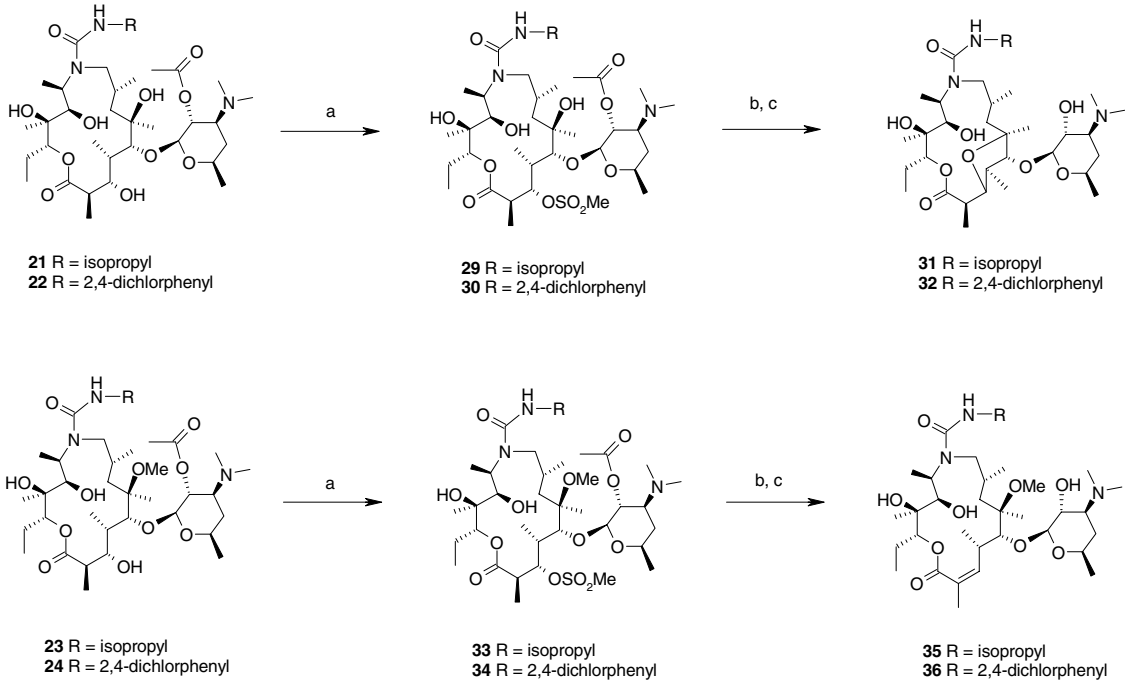
Scheme 3. Reagents and conditions: (a) EDC, DMSO, pyridinium trifluoroacetate; (b) MeOH, rt, 24 h.

Mass spectra of compounds **25** and **26** exhibited ions consistent with both hemiketal and keto structures. However, NMR data unambiguously revealed 3,6-hemiketal unit since the signal for C-3 is shifted from 75 to 103 ppm, while signal for C-3 in **27** and **28** is shifted from 79 ppm to 207 ppm indicating formation of ketone at C-3.

Introduction of mesyl group at position C-3 of 6-OH and 6-OMe derivatives **21**–**24** and subsequent base-promoted elimination afforded different products. Whereas 6-OH derivatives **21** and **22** produce 3,6-cyclic ethers **31** and **32**, 6-OMe derivatives **23** and **24** afford 2,3-anhydro derivatives **35** and **36**, respectively (Scheme 4). It is worth noting that in erythromycin series cyclic ethers were easily obtained[15] while anhydrolides were obtained only when the 'upper part' of the molecule was constrained via double bond between C-10 and C-11 or via C-11 to C-12 carbamate formation.[16]

Although mass spectra of compounds **31** and **32** showed molecular ions consistent with both cyclic ether and anhydro structures, missing double bond signal in NMR spectra and weak downfield shifting of C-3 (from 75 to 83 ppm) reveal 3,6-cyclic ether structure. Structures of anhydrolides **35** and **36** were also proved by NMR spectra. Shifting of signals for carbons C-2 from 45 to 146 ppm and C-3 from 79 to 127 ppm, respectively, as well as disappearance of signal for 2-H proton and strong downfield shift of 3-H were observed for both anhydrolide compounds.

Among already known 3-acylides of 14-membered macrolides, 3-*O*-(4-nitrophenyl)acetyl derivative of clarithromycin (TEA-0777) showed the best antibacterial



21 R = isopropyl
22 R = 2,4-dichlorphenyl

29 R = isopropyl
30 R = 2,4-dichlorphenyl

31 R = isopropyl
32 R = 2,4-dichlorphenyl

23 R = isopropyl
24 R = 2,4-dichlorphenyl

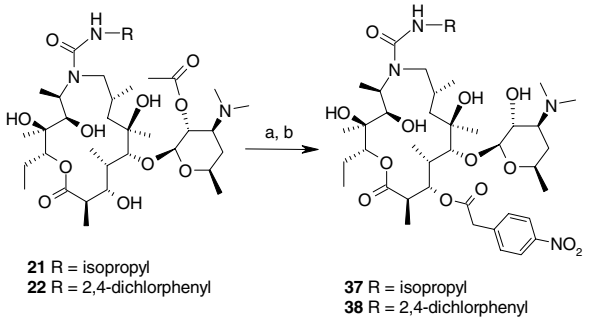
33 R = isopropyl
34 R = 2,4-dichlorphenyl

35 R = isopropyl
36 R = 2,4-dichlorphenyl

Scheme 4. Reagents and conditions: (a) methylsulfonyl anhydride, pyridine, rt, 3 h; (b) NaH, DMF/THF, 0 °C, 5 h then rt, 20 h; (c) MeOH, rt, 24 h.

activity.[17] Accordingly, we prepared 9a-carbamoyl acylides having (4-nitrophenyl)acetyl functionality attached to 3-*O* position (Scheme 5, compounds **37** and **38**) to test if antibacterial activity could be enhanced upon attachment of favorite side-arm. Compounds **21** and **22** were acylated using mixed anhydride obtained in situ from 4-nitrophenylacetic acid and pivaloyl chloride (Scheme 5). Subsequent methanolysis of 2′-*O*-acetyl group afforded 3-acylides **37** and **38**. Their structures were confirmed by NMR spectra as the signal for key proton H-3 is strongly shifted downfield from 3.9 to 5.4 ppm, while new carbonyl signal is found at 170 ppm along with other signals characteristic for 4-nitrophenyl moiety.

For all new compounds antibacterial activity was determined on a panel of various bacterial strains and compared to erythromycin (**2**). MIC values for *S. aureus*, *S. pneumoniae*, *S. pyogenes*, and *H. influenzae* strains are shown in Table 2. 3-Decladinosyl-6-hydroxy and 6-methoxy azalides **7** and **8** proved antibacterially inactive against these strains. Attachment of 9a-carbamoyl and 9a-thiocarbamoyl moieties bearing different alkyl and aryl groups (compounds **9**–**20**) did not increase antibacterial activity. Exception is weak activity of **19** against *S. pneumoniae*. Similar situation can be seen with 3,6-hemiketals **25**, **26** and 3,6-cyclic ethers **31**, **32**. However, anhydrolides **35** and **36** as well as ketolides **27** and **28** show good antibacterial activity against efflux resistant *S. pneumoniae*. The best antibacterial activity was shown by 9a-carbamoyl acylides **37** and **38** that possess 3-*O*-(4-nitrophenyl)acetyl group. Although they show rather weak activity against *H. influenzae*, their activity against efflux resistant *S. Pneumoniae* is better in comparison to erythromycin. Acylides **37** and **38** also show weak activity toward erythromycin-resistant *S. aureus*. Importantly, all compounds show no effect on eukaryotic organism *S. cerevisiae*.



Scheme 5. Reagents and conditions: (a) 4-nitrophenylacetic acid, pivaloyl chloride, TEA, pyridine, DCM, rt, 20 h; (b) MeOH, rt, 24 h.

3. Conclusion

Simple and efficient method for preparation of 9a-carbamoyl and 9a-thiocarbamoyl 3-decladinosyl 15-membered azalides **9**–**20** is developed. These derivatives bear various alkyl and aryl groups attached to azalide scaffold through urea or thiourea linkage at 9a-position. The conformation of these derivatives in solution is C-3 to C-5 'folded out'. They are also starting compounds for the successful chemical transformation of hydroxyl group at position C-3 affording ketolides, hemiketals, cyclic ethers, acylides, and first 2,3-anhydrolides of 15-membered macrolides. 3-Acyl, 3-keto, and 2,3-anhydro carbamoyl derivatives of 15-membered azalides show moderate activity against resistant pathogens. As the structure-activity relationship of 3-decladinosyl derivatives of 15-membered azalides is far less established in contrast to 14-membered analogs, our results provide new insight into the antibacterial activity of azalides that will certainly help us and others in envisioning new antibacterial agents.

4. Experimental

All solvents and reagents were used as supplied, unless noted otherwise. IR spectra were recorded on Nicolet Magna-IR 760 FT-IR spectrometer (KBr). Mass spectra were recorded on Varian MAT 311 instrument (FAB), and Platform LCZ or LCQ Deca instruments (ESI). HRMS (ESI) were recorded on Micromass Qtof2. NMR spectra were recorded as $CDCl_3$ solution at Varian Unity Inova 600, Bruker Advance DRX 500, and Bruker Advance 300 spectrometers with trimethylsilane as an internal standard. For characterization of complex organic structures one-dimensional (1D) (^1H, ^{13}C, and APT) and two-dimensional (2D) (COSY, HETCOR, HMBC) NMR techniques were used. Reactions were monitored by thin layer chromatography on silica gel plates (Merck Silica gel 60 F_{254}). Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus.

Table 2. In vitro antibacterial activities of prepared macrolides

Strain	MIC (μg/ml)															
	2	**6**	**9–18**	**19**	**20**	**25**	**26**	**27**	**28**	**31**	**32**	**35**	**36**	**37**	**38**
S. aureus-M	>64	>64	>64	>64		>64		>64		>64		>64		>64	32
S. aureus-cMLS	>64	>64	>64	>64		>64		>64		>64		>64		>64	32
S. pneumoniae	0.125	0.5	>64	32	>64	>64		8	8	>64		8	8	0.5	2
S. pneumoniae-M	8	16	>64	>64		>64		64	8	>64		>64	16	4	4
S. pyogenes	0.125	1	>64	>64		>64		16	16	>64		16	32	2	4
S. pyogenes-M	8	16	>64	>64		>64		>64		>64		>64		32	32
H. influenzae	4	8	>64	>64		>64		>64		>64		>64		16	32

MICs were determined on a TECAN Genesis 150 instrument using micro-dilution method and Mueller–Hinton media for bacterial growth.

4.1. 3-Decladinosyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A (7)

Compound **5**[7] (2.00 g, 2.71 mmol) was suspended in water (20 ml) and the pH was adjusted to 1 using 6 N HCl. The reaction mixture was stirred for 24 h at room temperature, CH_2Cl_2 (10 ml) was added, and pH adjusted to 8. The layers were separated and aqueous layer extracted with CH_2Cl_2 (2 × 10 ml). Combined organic extracts were rinsed with saturated aqueous $NaHCO_3$ solution, brine, and water, and dried over Na_2CO_3. The solvent was evaporated to afford **7** (1.23 g, 79%) as a white solid, mp 110–115 °C.

IR (KBr) 3444, 2972, 2937, 2877, 1716, 1638, 1458, 1380, 1348, 1266, 1169, 1112, 1074, 1049, 957, 899, 862, 835, 706, 652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (13-H), 4.47 (1′-H), 3.80 (3-H), 3.48 (11-H), 3.61 (5-H), 3.54 (5′-H), 3.27 (2′-H), 3.09 (9a-H), 2.64 (2-H), 2.58 (10-H), 2.51 (3′-H), 2.24 (3′-N(CH_3)$_2$), 2.23 (4-H), 1.91 (14a-H), 1.78 (8-H), 1.81 (9b-H), 1.66 (4′a-H), 1.54 (7a-H), 1.52 (14b-H), 1.42 (7b-H), 1.29 (6-CH_3), 1.32 (2-CH_3), 1.24 (5′-CH_3), 1.27 (4′b-H), 1.15 (12-CH_3), 1.08 (10-CH_3), 1.05 (4-CH_3), 0.94 (8-CH_3), 0.88 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1 (1-C), 106.2 (1′-C), 94.4 (5-C), 78.8 (3-C), 77.1 (13-C), 73.6 (11-C), 73.2 (12-C), 73.0 (6-C), 70.2 (2′-C), 69.5 (5′-C), 65.2 (3′-C), 57.4 (10-C), 56.5 (9-C), 44.0 (2-C), 40.6 (7-C), 39.9 (3′N-(CH_3)$_2$), 35.5 (4-C), 28.8 (8-C), 27.7 (4′-C), 25.7 (6-CH_3), 20.2 (8-CH_3), 20.7 (5′-CH_3), 20.6 (14-C), 15.8 (2-CH_3), 15.6 (12-CH_3), 13.4 (10-CH_3), 10.3 (15-CH_3), 7.5 (4-CH_3); MS (ES) 577.7 ($M+H^+$).

4.2. 3-Decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A (8)

Compound **6**[18] (1.77 g, 2.36 mmol) was suspended in water (20 ml) and the pH was adjusted to 1 using 6 N HCl. The reaction mixture was stirred for 24 h at room temperature, CH_2Cl_2 (10 ml) was added, and pH adjusted to 8. The layers were separated and aqueous layer extracted with CH_2Cl_2 (2 × 10 ml). Combined organic extracts were rinsed with saturated aqueous $NaHCO_3$ solution, brine, and water, and dried over Na_2CO_3. The solvent was evaporated to afford **8** (0.64 g, 46%) as a white solid, mp 93–97 °C.

IR (KBr) 3423, 2973, 2936, 2874, 1728, 1686, 1655, 1638, 1560, 1541, 1508, 1459, 1380, 1270, 1166, 1112, 1075, 1044, 1003, 984, 973, 896, 836, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (13-H), 4.49 (1′-H), 3.70 (3-H), 3.44 (11-H), 3.81 (5-H), 3.53 (5′-H), 3.22 (6-OCH_3), 3.25 (2′-H), 2.98 (9a-H), 2.66 (2-H), 2.61 (10-H), 2.49 (3′-H), 2.25 (3′-N(CH_3)$_2$), 2.18 (4-H), 1.93 (14a-H), 1.88 (8-H), 1.88 (9b-H), 1.66 (4′a-H), 1.51 (7a-H), 1.50 (14b-H), 1.33 (7b-H), 1.33 (18-CH_3), 1.31 (16-CH_3), 1.25 (5′-CH_3), 1.25 (4′b-H), 1.11 (21-CH_3), 1.07 (20-CH_3), 1.06 (17-CH_3), 0.96 (19-CH_3), 0.87 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3 (1-C), 106.6 (1′-C), 89.0 (5-C), 78.8 (6-C), 78.5 (3-C), 77.4 (13-C), 74.2 (11-C), 73.9 (12-C), 70.3 (2′-C), 69.9 (5′-C), 65.6 (3′-C), 58.4 (9-C), 58.2 (10-C), 49.9 (6-OCH_3), 44.5 (2-C), 40.1 (3′N-(CH_3)$_2$), 40.1 (7-C), 35.5 (4-C), 27.8 (4′-C), 27.7 (8-C), 21.3 (19-CH_3), 21.1 (5′-CH_3), 20.7 (14-C), 20.5 (15-CH_3), 18.7 (18-CH_3), 16.0 (21-CH_3), 16.0 (16-CH_3), 13.4 (20-CH_3), 7.8 (17-CH_3); MS (ES) 591.7 ($M+H^+$).

4.3. 9a-Carbamoyl and 9a-thiocarbamoyl 3-decladinosyl-6-hydroxy derivatives (9–18)

4.3.1. General procedure. To the solution of compound **7** in toluene (c = 0.05 g/ml) corresponding isocyanate or isothiocyanate was added. Reaction mixture was stirred at room temperature. After removal of solvent under reduced pressure crude residue was obtained. Crystallization from a mixture of acetone–petrol ether or ethyl ether–petrol ether afforded products **9**–**18** (Table 3).

4.4. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (9)

White solid, mp 140–145 °C. IR (KBr) 3498, 3466, 2974, 2938, 2877, 1726, 1618, 1596, 1528, 1458, 1373, 1279, 1172, 1111, 1082, 1036, 978, 956, 932, 901, 833, 776, 689, 633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.03 (13-H), 4.40 (1′-H), 4.37 (9a-NCON′H), 3.92 (1″-H), 3.89 (3-H), 3.50 (11-H), 3.69 (5′-H), 3.63 (5-H), 3.32 (2′-H), 2.60 (2-H), 2.54 (3′-H), 2.28 (3′-N(CH_3)$_2$), 1.88 (14-Ha), 1.72 (4′-Ha), 1.58 (14-Hb), 1.56 (4-H), 1.34 (4′-Hb), 1.29 (2-CH_3),

Table 3. 9a-Carbamoyl and 9a-thiocarbamoyl 3-decladinosyl derivatives

Compound	X=C=N–R		Solvent	Time	Product	Yield
	X	R				
7 (1 g/1.73 mmol)	O	Isopropyl (0.17 g/1.9 mmol)	Toluene	1 h	**9**	0.97 g (84%)
7 (1 g /1.73 mmol)	O	Ethyl (0.17 g/2.46 mmol)	Toluene	1 h	**10**	0.98 g (87%)
7 (1 g/1.73 mmol)	O	*tert*-Butyl (0.2 g/2.0 mmol)	Toluene	1 h	**11**	0.95 g (81%)
7 (1 g/1.73 mmol)	O	Benzyl (0.25 g/1.9 mmol)	Toluene	1 h	**12**	0.82 g (66%)
7 (1 g/1.73 mmol)	O	3-Trifluoromethylphenyl (0.33 g/2.0 mmol)	Toluene	30 min	**13**	0.98 g (74%)
7 (1 g/1.73 mmol)	O	2-Trifluoromethylphenyl (0.35 g/2.0 mmol)	Toluene	30 min	**14**	0.84 g (63%)
7 (1 g/1.73 mmol)	S	3-Trifluoromethylphenyl (0.35 g/2.0 mmol)	Toluene	15 min	**15**	0.98 g (68%)
7 (1 g/1.73 mmol)	S	Benzyl (0.38 g/1.9 mmol)	Toluene	1 h	**16**	1.06 g (84%)
7 (3 g/5.19 mmol)	O	2,4-Dichlorphenyl (1.07 g/5.7 mmol)	Toluene	1 h	**17**	2.46 g (62%)
7 (1 g/1.73 mmol)	S	Allyl (0.19 g/1.9 mmol)	Toluene	5 h	**18**	0.72 g (61%)

1.27 (5′-CH_3), 1.26 (10-CH_3), 1.13 (1″-$(CH_3)_2$), 1.10 (12-CH_3), 1.06 (8-CH_3), 0.93 (4-CH_3), 0.89 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3 (1-C), 158.8 (9a-N<u>C</u>ONH), 105.8 (1′-C), 95.9 (5-C), 77.7 (13-C), 77.1 (12-C), 74.5 (11-C), 74.9 (3-C), 74.2 (6-C), 73.0 (9-C), 70.3 (5′-C), 69.2 (2′-C), 64.9 (3′-C), 44.6 (2-C), 42.4 (1″-C), 41.7 (7-C), 39.9 (3′-$N(CH_3)_2$), 38.5 (4-C), 27.6 (4′-C), 25.8 (6-CH_3), 23.1 (1″-$(CH_3)_2$), 21.2 (14-C), 20.6 (5′-CH_3), 19.4 (8-CH_3), 16.6 (12-CH_3), 15.9 (2-CH_3), 12.2 (10-CH_3), 10.0 (15-CH_3), 7.7 (4-CH_3); MS (FAB) 662 ($M+H^+$); HRMS (ES) calcd for $C_{33}H_{63}N_3O_{10}$ ($M+H^+$) 662.4592, found 662.4562.

4.5. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-ethylcarbamoyl)-9a-aza-9a-homoerythromycin A (10)

White solid, mp 130–136 °C. IR (KBr) 3433, 2975, 2936, 2878, 1730, 1618, 1532, 1458, 1382, 1350, 1267, 1172, 1111, 1077, 1036, 980, 956, 933, 900, 834, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (13-H), 4.39 (1′-H), 4.56 (9a-NCON′<u>H</u>), 3.86 (3-H), 3.57 (11-H), 3.68 (5′-H), 3.62 (5-H), 3.43 (9-Ha), 3.31 (2′-H), 3.23 (N′C<u>H</u>$_2$), 2.59 (2-H), 2.53 (3′-H), 2.47 (9-Hb), 2.27 (3′-$N(CH_3)_2$), 1.90 (14-Ha), 1.71 (4′-Ha), 1.55 (14-Hb), 1.55 (4-H), 1.33 (4′-Hb), 1.28 (2-CH_3), 1.28 (15-CH_3), 1.28 (10-CH_3), 1.27 (5′-CH_3), 1.11 (N′CH_2C<u>H</u>$_3$), 1.08 (12-CH_3), 1.05 (8-CH_3), 0.92 (4-CH_3), 0.87 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0 (1-C), 159.5 (9a-N<u>C</u>ONH), 105.7 (1′-C), 96.2 (5-C), 77.7 (13-C), 77.1 (12-C), 74.5 (11-C), 75.1 (3-C), 74.1 (6-C), 72.8 (9-C), 70.3 (5′-C), 69.2 (2′-C), 64.9 (3′-C), 44.7 (2-C), 41.1 (7-C), 39.9 [3′N-$(CH_3)_2$], 38.3 (4-C), 36.5 (N′<u>C</u>H$_2$), 28.9 (8-C), 27.6 (4′-C), 25.6 (6-CH_3), 21.3 (14-C), 20.6 (5′-CH_3), 19.3 (8-CH_3), 16.6 (12-CH_3), 15.8 (2-CH_3), 15.0 (N′CH_2<u>C</u>H$_3$), 12.1 (10-CH_3), 10.3 (15-CH_3), 7.6 (4-CH_3); MS (FAB) 648 ($M+H^+$); HRMS (ES) calcd for $C_{32}H_{61}N_3O_{10}$ ($M+H^+$) 648.4435, found 648.4430.

4.6. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-*t*-butylcarbamoyl)-9a-aza-9a-homoerythromycin A (11)

White solid, mp 168–172 °C. IR (KBr) 3497, 2976, 2946, 1725, 1626, 1532, 1456, 1364, 1346, 1317, 1281, 1175, 1112, 1082, 1055, 1034, 977, 956, 931, 901, 865, 776, 685, 634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (13-H), 4.52 (9a-NCON′<u>H</u>), 4.41 (1′-H), 3.89 (3-H), 3.68 (5′-H), 3.47 (11-H), 3.62 (5-H), 3.41 (9-Ha), 3.32 (2′-H), 2.59 (2-H), 2.54 (3′-H), 2.28 (3′-$N(CH_3)_2$), 1.88 (14-Ha), 1.72 (4′-Ha), 1.57 (14-Hb), 1.56 (4-H), 1.32 (4′-Hb), 1. 31 (N′C(C<u>H</u>$_3$)$_3$), 1.30 (2-CH_3), 1.28 (5′-CH_3), 1.24 (10-CH_3), 1.11 (12-CH_3), 1.05 (8-CH_3), 0.92 (4-CH_3), 0.88 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7 (1-C), 158.7 (9a-N<u>C</u>ONH), 105.9 (1′-C), 95.7 (5-C), 77.9 (13-C), 77.1 (12-C), 74.6 (11-C), 74.8 (3-C), 74.3 (6-C), 73.3 (9-C), 70.3 (5′-C), 69.2 (2′-C), 65.0 (3′-C), 50.8 (N′<u>C</u>$(CH_3)_3$), 44.6 (2-C), 41.1 (7-C), 40.0 (3′N-$(CH_3)_2$), 38.6 (4-C), 29.1 (N′C(<u>C</u>H$_3$)$_3$), 28.9 (8-C), 27.7 (4′-C), 26.2 (6-CH_3), 21.2 (14-C), 20.6 (5′-CH_3), 19.4 (8-CH_3), 16.5 (12-CH_3), 16.0 (2-CH_3), 12.2 (10-CH_3), 10.6 (15-CH_3), 7.8 (4-CH_3); MS (FAB) 676 ($M+H^+$); HRMS (ES) calcd for $C_{34}H_{65}N_3O_{10}$ ($M+H^+$) 676.4748, found 676.4711.

4.7. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-benzylcarbamoyl)-9a-aza-9a-homoerythromycin A (12)

White solid, mp 147–152 °C. IR (KBr) 3404, 2975, 2936, 1731, 1625, 1529, 1454, 1384, 1349, 1319, 1274, 1172, 1111, 1091, 1049, 978, 957, 931, 900, 865, 837, 740, 700, 635 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (4″-H, 6″-H), 7.30 (3″-H, 7″-H), 7.24 (5″-H), 5.03 (13-H), 4.55 (1″-Ha), 4.48 (9a-NCON′<u>H</u>), 4.30 (1′-H), 4.30 (1″-Hb), 3.89 (3-H), 3.68 (5′-H), 3.51 (11-H), 3.62 (5-H), 3.41 (9-Ha), 3.30 (2′-H), 2.62 (2-H), 2.30 (3′-H), 2.27 (3′-$N(CH_3)_2$), 1.89 (14-Ha), 1.69 (4′-Ha), 1.58 (14-Hb), 1.56 (4-H), 1.28 (4′-Hb), 1.30 (2-CH_3), 1.27 (5′-CH_3), 1.32 (10-CH_3), 1.28 (6-CH_3), 1.10 (12-CH_3), 1.04(8-CH_3), 0.93 (4-CH_3), 0.89 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) [δ/ppm] 176.9 (1-C), 159.6 (9a-N<u>C</u>ONH), 139.4 (2″-C), 128.6 (4″-C, 6″-C), 127.3 (3″-C, 7″-C), 126.9 (5″-C), 105.7 (1′-C), 96.4 (5-C), 77.7 (13-C), 77.1 (12-C), 75.0 (11-C), 75.0 (3-C), 74.2 (6-C), 74.4 (9-C), 70.2 (5′-C), 69.2 (2′-C), 64.8 (3′-C), 44.7 (2-C), 44.6 (1″-C), 44.6 (7-C), 40.0 (3′N-$(CH_3)_2$), 38.4 (4-C), 27.5 (4′-C), 25.3 (6-CH_3), 21.3 (14-C), 20.7 (5′-CH_3), 19.7 (8-CH_3), 16.7 (12-CH_3), 15.9 (2-CH_3), 12.2 (10-CH_3), 10.4 (15-CH_3), 7.6 (4-CH_3); MS (ES) 710.6 ($M+H^+$); HRMS (ES) calcd for $C_{37}H_{63}N_3O_{10}$ ($M+H^+$) 710.4592, found 710.4578.

4.8. 3-Decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(3-trifluoromethylphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (13)

White solid, mp 133–139 °C. IR (KBr) 3451, 2975, 2935, 1727, 1704, 1659, 1548, 1494, 1449, 1384, 1336, 1258, 1167, 1125, 1072, 1049, 979, 957, 933, 901, 864, 835, 794, 758, 699, 659 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (2″-H), 7.58 (6″-H), 7.35 (5″-H), 7.23 (4″-H), 4.82 (13-H), 4.62 (9a-NCON′<u>H</u>), 4.35 (1′-H), 3.87 (3-H), 3.62 (5′-H), 3.62 (5-H), 3.51 (11-H), 3.41 (9-Ha), 3.30 (2′-H), 2.66 (2-H), 2.50 (3′-H), 2.26 (3′-$N(CH_3)_2$), 1.88 (14-Ha), 1.71 (4′-Ha), 1.58 (14-Hb), 1.56 (4-H), 1.28 (6-CH_3), 1.28 (2-CH_3), 1.31 (4′-Hb), 1.27 (5′-CH_3), 1.24 (10-CH_3), 1.10 (12-CH_3), 1.04 (8-CH_3), 0.92 (4-CH_3), 0.88 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (1-C), 156.6 (9a-N<u>C</u>ONH), 140.0 (1″-C), 131.3 (3″-C), 129.2 (5″-C), 122.3 (6″-C), 118.9 (4″-C), 115.8 (2″-C), 106.1 (1′-C), 96.5 (5-C), 78.8 (13-C), 77.1 (12-C), 75.7 (3-C), 74.8 (9-C), 74.7 (6-C), 74.6 (11-C), 70.6 (5′-C), 69.4 (2′-C), 65.2 (3′-C), 45.2 (2-C), 40.2 (3′N-$(CH_3)_2$), 38.8 (4-C), 27.9 (4′-C), 21.5 (14-C), 20.9 (5′-CH_3), 20.0 (8-CH_3), 16.8 (12-CH_3), 16.1 (2-CH_3), 13.8 (10-CH_3), 10.9 (15-CH_3), 7.7 (4-CH_3); MS (ES) 764.6 ($M+H^+$); HRMS (ES) calcd for $C_{37}H_{60}F_3N_3O_{10}$ ($M+H^+$) 764.4309, found 764.4281.

4.9. 3-Decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(2-trifluoromethylphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (14)

White solid, mp 125–130 °C. IR (KBr) 3458, 2975, 2940, 2879, 2786, 1727, 1658, 1591, 1536, 1457, 1384, 1322, 1282, 1244, 1171, 1112, 1035, 979, 956, 934, 901, 864, 834, 762, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (6″-H), 7.55 (3″-H), 7.26 (4″-H), 7.16 (5″-H), 4.98 (13-H), 4.62 (9a-NCON′<u>H</u>), 4.38 (1′-H), 3.90 (3-H),

3.65 (5′-H), 3.64 (5-H), 3.61 (11-H), 3.31 (2′-H), 2.64 (2-H), 2.52 (3′-H), 2.27 (3′-N(CH_3)$_2$), 1.91 (14-Ha), 1.72 (4′-Ha), 1.57 (14-Hb), 1.56 (4-H), 1.35 (10-CH_3), 1.32 (2-CH_3), 1.28 (6-CH_3), 1.31 (4′-Hb), 1.24 (5′-CH_3), 1.15 (12-CH_3), 1.10 (8-CH_3), 0.96 (4-CH_3), 0.91 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3 (1-C), 157.0 (9a-N<u>C</u>ONH), 136.4 (1″-C), 132.5 (3″-C), 125.7 (5″-C), 125.1 (4″-C), 123.4 (6″-C), 105.9 (1′-C), 82.9 (5-C), 77.9 (13-C), 74.4 (12-C), 75.2 (3-C), 74.4 (6-C), 73.8 (11-C), 70.4 (5′-C), 69.2 (2′-C), 64.9 (3′-C), 44.7 (2-C), 39.9 (3′N-(CH_3)$_2$), 38.6 (4-C), 27.6 (4′-C), 21.3 (14-C), 20.7 (5′-CH_3), 19.1 (8-CH_3), 16.6 (12-CH_3), 15.9 (2-CH_3), 12.5 (10-CH_3), 10.5 (15-CH_3), 7.7 (4-CH_3); MS (FAB) 764.3 (M+H$^+$); HRMS (ES) calcd for $C_{37}H_{60}F_3N_3O_{10}$ (M+H$^+$) 764.4309, found 764.4298.

4.10. 3-Decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(3-trifluoromethylphenyl)thiocarbamoyl]-9a-aza-9a-homoerythromycin A (15)

White solid, mp 118–124 °C. IR (KBr) 3449, 2975, 2937, 1708, 1600, 1547, 1494, 1452, 1384, 1328, 1255, 1164, 1116, 1073, 1019, 980, 956, 885, 862, 793, 735, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (2″-bH), 7.42 (6″-H), 7.26 (5″-H), 7.18 (4″-H), 4.82 (13-H), 4.61 (9a-NCON′<u>H</u>), 4.40 (1′-H), 3.90 (3-H), 3.66 (5′-H), 3.57 (5-H), 3.49 (11-H), 3.31 (2′-H), 2.69 (2-H), 2.52 (3′-H), 2.27 (3′-N(CH_3)$_2$), 1.95 (14-Ha), 1.69 (4′-Ha), 1.62 (14-Hb), 1.53 (4-H), 1.34 (2-CH_3), 1.28 (6-CH_3), 1.34 (4′-Hb), 1.28 (5′-CH_3), 1.25 (10-CH_3), 1.21 (12-CH_3), 1.08 (8-CH_3), 0.98 (4-CH_3), 0.94 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.2 (9a-N<u>C</u>ONH), 177.6 (1-C), 140.4 (1″-C), 130.5 (3″-C), 130.2 (5″-C), 128.1 (6″-C), 125.2 (4″-C), 123.6 (2″-C), 105.2 (1′-C), 94.9 (5-C), 79.3 (3-C), 77.7 (13-C), 77.2 (12-C), 73.5 (9-C), 73.6 (6-C), 73.4 (11-C), 70.6 (5′-C), 69.5 (2′-C), 65.2 (3′-C), 44.5 (2-C), 41.1 (7-C), 40.2 (3′N-(CH_3)$_2$), 38.8 (4-C), 28.1 (8-C), 27.9 (4′-C), 25.9 (6-CH_3), 21.0 (14-C), 21.0 (5′-CH_3), 18.9 (8-CH_3), 16.6 (12-CH_3), 16.1 (2-CH_3), 12.8 (10-CH_3), 10.8 (15-CH_3), 7.6 (4-CH_3); MS (FAB) 780 (M+H$^+$); HRMS (ES) calcd for $C_{37}H_{60}F_3N_3O_9S$ (M+H$^+$) 780.4081, found 780.4036.

4.11. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-benzylthiocarbamoyl)-9a-aza-9a-homoerythromycin A (16)

White solid, mp 125–132 °C. IR (KBr) 3448, 2974, 2938, 1703, 1528, 1456, 1384, 1323, 1283, 1178, 1109, 1073, 1020, 978, 955, 934, 862, 825, 759, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (4″-H, 6″-H), 7.30 (3″-H, 7″-H), 7.27 (5″-H), 4.64 (9a-NCSN′<u>H</u>), 4.57 (13-H), 4.39 (1′-H), 3.89 (3-H), 3.67 (5′-H), 3.67 (5-H), 3.51 (11-H), 3.31 (2′-H), 2.64 (2-H), 2.55 (3′-H), 2.28 (3′-N(CH_3)$_2$), 1.93 (14-Ha), 1.73 (4′-Ha), 1.62 (14-Hb), 1.56 (4-H), 1.34 (2-CH_3), 1.27 (4′-Hb), 1.27 (5′-CH_3), 1.27 (10-CH_3), 1.25 (12-CH_3), 0.94 (8-CH_3), 0.87 (4-CH_3), 0.86 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2 (9a-N<u>C</u>SNH), 179.5 (1-C), 137.5 (2″-C), 128.6 (4″-C, 6″-C), 128.2 (3″-C, 7″-C), 127.6 (5″-C), 105.9 (1′-C), 93.9 (5-C), 78.7 (13-C), 75.1 (12-C), 75.2 (6-C), 74.6 (3-C), 73.9 (11-C), 70.1 (5′-C), 69.5 (2′-C), 65.2 (3′-C), 50.8 (1″-C), 44.1 (2-C), 40.2 (3′N-(CH_3)$_2$), 44.4 (4-C), 27.9 (4′-C), 21.1 (14-C), 20.9 (5′-CH_3), 19.0 (8-Me), 16.7 (12-CH_3), 16.5 (2-CH_3), 12.3 (10-CH_3), 11.3 (15-CH_3), 8.3 (4-CH_3); MS (ES) 726.5 (M+H$^+$); HRMS (ES) calcd for $C_{37}H_{63}N_3O_9S$ (M+H$^+$) 726.4363, found 726.4343.

4.12. 3-Decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (17)

White solid, mp 138–149 °C. IR (KBr) 3428, 2973, 2934, 2878, 1718, 1659, 1580, 1517, 1459, 1382, 1345, 1297, 1229, 1176, 1110, 1086, 1048, 978, 955, 932, 901, 866, 825, 759, 731, 696, 631 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (6″-H), 7.33 (3″-H), 7.17 (5″-H), 4,71 (13-H), 4.57 (9a-NCON′<u>H</u>), 4.40 (1′-H), 4.10 (5-H), 3.89 (3-H), 3.89 (5′-H), 3.32 (2′-H), 2.62 (2-H), 2.60 (3′-H), 2.30 (3′-N(CH_3)$_2$), 1.93 (14-Ha), 1.76 (4′-Ha), 1.57 (14-Hb), 1.56 (4-H), 1.53 (12-CH_3), 1.36 (10-CH_3), 1.31 (2-CH_3), 1.29 (4′-Hb), 1.29 (8-CH_3), 1.27 (5′-CH_3), 0.94 (4-CH_3), 0.90 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2 (1-C), 156.4 (9a-N<u>C</u>ONH), 134.7 (1″-C), 128.4 (3″-C), 127.6 (2″-C), 125.3 (5″-C), 123.2 (4″-C), 105.9 (1′-C), 78.2 (13-C), 75.9 (3-C), 70.5 (5′-C), 69.5 (2′-C), 65.2 (3′-C), 44.9 (2-C), 40.2 (3′N-(CH_3)$_2$), 38.8 (4-C), 28.1 (4′-C), 28.0 (8-C), 21.5 (14-C), 20.9 (5′-CH_3), 19.4 (6-CH_3), 16.8 (12-CH_3), 16.2 (2-CH_3), 12.9 (10-CH_3), 10.9 (15-CH_3), 8.0 (4-CH_3); MS (ES) 764.5 (M+H$^+$); HRMS (ES) calcd for $C_{36}H_{59}Cl_2N_3O_{10}$ (M+H$^+$) 764.3656, found 764.3627.

4.13. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-allylthiocarbamoyl)-9a-aza-9a-homoerythromycin A (18)

White solid, mp 116–121 °C. IR (KBr) 3451, 2974, 2938, 2878, 1704, 1644, 1520, 1456, 1384, 1321, 1286, 1178, 1110, 1074, 1048, 1019, 978, 955, 934, 862, 833, 762, 632 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (2″-H), 5.29 (3″-Ha), 5.20 (3″-Hb), 4.57 (13-H), 4.41 (1′-H), 4.37 (9a-NCSN′<u>H</u>), 4.34 (1″-Ha), 4.21 (1″-Hb), 3.90 (3-H), 3.69 (5′-H), 3.78 (5-H), 3.32 (2′-H), 2.64 (2-H), 2.54 (3′-H), 2.28 (3′-N(CH_3)$_2$), 1.92 (14-Ha), 1.70 (4′-Ha), 1.60 (14-Hb), 1.52 (4-H), 1.34 (4′-Hb), 1.35 (2-CH_3), 1.28 (5′-CH_3), 1.28 (6-CH_3), 1.26 (10-CH_3), 1.24 (12-CH_3), 1.12 (8-CH_3), 0.95 (4-CH_3), 0.94 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3 (1-C), 179.7 (9a-N<u>C</u>SNH), 133.6 (2″-C), 117.8 (3″-C), 106.0 (1′-C), 95.0 (5-C), 78.6 (13-C), 75.1 (12-C), 75.1 (6-C), 74.8 (3-C), 73.8 (11-C), 70.4 (5′-C), 69.3 (2′-C), 65.4 (3′-C), 48.8 (1″-C), 44.2 (2-C), 39.9 (3′N-(CH_3)$_2$), 38.9 (4-C), 27.6 (4′-C), 20.7 (14-C), 20.6 (5′-CH_3), 18.7 (8-CH_3), 16.4 (12-CH_3), 16.2 (2-CH_3), 12.1 (10-CH_3), 10.9 (15-CH_3), 7.9 (4-CH_3); MS (ES) 676.4 (M+H$^+$); HRMS (ES) calcd for $C_{33}H_{61}N_3O_9S$ (M+H$^+$) 676.4207, found 676.4181.

4.14. 9a-Carbamoyl 3-decladinosyl-6-methoxy derivatives (19, 20)

4.14.1. General procedure. To the solution of **8** in acetonitrile (c = 0.01 g/ml) corresponding isocyanate was added. Reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated and the crude product purified by chromatography on a silica gel column using CH_2Cl_2:MeOH:NH_4OH (90:5:0.5) as an eluent (Table 4).

Table 4. 9a-Carbamoyl 3-decladinosyl 6-methoxy derivatives

Compound	X=C=N–R		Solvent	Time	Product	Yield
	X	R				
8 (0.2 g/0.33 mmol)	O	Isopropyl (0.07 ml/0.67 mmol)	Acetonitrile	2 h	**19**	0.13 g (56%)
8 (0.2 g/0.33 mmol)	O	2,4-Dichlorphenyl (0.064 g/0.33 mmol)	Acetonitrile	30 min	**20**	0.17 g (63%)

4.15. 3-Decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (19)

White solid, mp 154–159 °C. IR (KBr) 3424, 2975, 2937, 2877, 1732, 1687, 1627, 1562, 1525, 1460, 1379, 1270, 1166, 1112, 1080, 1053, 984, 958, 938, 896, 828, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (13-H), 4.44 (1′-H), 3.91 (1″-H), 3.65 (3-H), 3.73 (5-H), 3.53 (5′-H), 3.23 (2′-H), 3.14 (6-OCH_3), 2.61 (2-H), 2.48 (3′-H), 2.25 (3′-$N(CH_3)_2$), 1.82 (4-H), 1.91 (14a-H), 2.03 (8-H), 1.66 (4′a-H), 1.49 (14b-H), 1.35 (18-CH_3), 1.28 (16-CH_3), 1.25 (20-CH_3), 1.25 (5′-CH_3), 1.25 (4′b-H), 1.15 (1″-$(CH_3)_2$), 1.14 (21-CH_3), 1.05 (17-CH_3), 0.96 (19-CH_3), 0.88 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8 (1-C), 155.1 (9a-NCONH), 106.6 (1′-C), 90.2 (5-C), 79.5 (6-C), 78.9 (3-C), 74.2 (11-C), 74.7 (12-C), 70.5 (2′-C), 70.0 (5′-C), 65.7 (3′-C), 49.8 (6-OCH_3), 44.8 (2-C), 42.7 (1″-C), 40.3 (3′N-$(CH_3)_2$), 36.4 (4-C), 28.1 (4′-C), 27.5 (8-C), 23.6 (18-CH_3), 23.3 (1″-$(CH_3)_2$), 22.3 (14-C), 21.3 (5′-CH_3), 20.6 (19-CH_3), 16.9 (21-CH_3), 15.5 (16-CH_3), 12.6 (20-CH_3), 11.2 (15-CH_3), 7.7 (17-CH_3); MS (ES) 676.8 ($M+H^+$); HRMS (ES) calcd for $C_{34}H_{65}N_3O_{10}$ ($M+H^+$) 676.4748, found 676.4711.

4.16. 3-Decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (20)

White solid, mp 123–127 °C. IR (KBr) 3448, 2975, 2939, 2879, 2787, 1729, 1707, 1670, 1582, 1517, 1459, 1382, 1328, 1298, 1274, 1165, 1112, 1076, 1051, 983, 956, 937, 897, 861, 822, 750, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (6″-H), 7.34 (3″-H), 7.18 (5″-H), 5.11 (13-H), 4.39 (1′-H), 3.81 (5-H), 3.72 (3-H), 3.52 (5′-H), 3.35 (6-OCH_3), 3.18 (2′-H), 2.61 (2-H), 2.61 (10-H), 2.50 (3′-H), 2.27 (3′-$N(CH_3)_2$), 2.04 (8-H), 1.93 (14a-H), 1.89 (4-H), 1.68 (4′a-H), 1.52 (14b-H), 1.35 (6-CH_3), 1.33 (4′b-H), 1.28 (2-CH_3), 1.25 (10-CH_3), 1.23 (5′-CH_3), 1.18 (12-CH_3), 1.04 (4-CH_3), 1.02 (8-CH_3), 0.89 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3 (1-C), 155.0 (9a-NCONH), 134.9 (1″-C), 128.4 (3″-C), 127.7 (5″-C), 127.1 (2″-C), 122.7 (4″-C), 122.1 (6″-C), 106.9 (1′-C), 90.3 (5-C), 79.7 (3-C), 79.1 (6-C), 76.1 (13-C), 73.6 (11-C), 73.6 (12-C), 70.5 (2′-C), 69.9 (5′-C), 65.7 (3′-C), 49.9 (6-O-CH_3), 44.7 (2-C), 40.3 (3′N-$(CH_3)_2$), 36.7 (4-C), 35.5 (7-C), 28.3 (4′-H), 28.2 (8-C), 22.4 (14-C), 21.3 (5′-CH_3), 20.6 (18-CH_3), 16.9 (21-CH_3), 15.4 (16-CH_3), 20.5 (20-CH_3), 11.4 (15-CH_3), 7.6 (17-CH_3); MS (ES) 778.6 ($M+H^+$); HRMS (ES) calcd for $C_{37}H_{61}Cl_2N_3O_{10}$ ($M+H^+$) 778.3812, found 778.3778.

4.17. Acetylation of 2′-OH (derivatives 21–24)

4.17.1. General procedure. To a solution of 2′-OH derivatives **7**, **9**, **17**, and **19** in CH_2Cl_2 (c = 0.05 g/ml), $NaHCO_3$ (4.5 eq) and acetic anhydride (1.1 eq) were added and the mixture stirred for 24 h at room temperature. Into the reaction mixture saturated aqueous $NaHCO_3$ solution was added, the layers were separated, and the aqueous layer extracted two more times with CH_2Cl_2. Combined organic extracts were rinsed with saturated aqueous $NaHCO_3$ solution and water, and evaporated yielding **21**–**24** that are used without further purifications.

4.18. 2′-*O*-Acetyl-3-decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (21)

According to general procedure 1 g of **9** (1.51 mmol) afforded **21** (1.10 g, quant).

IR (KBr) 3423, 2974, 2938, 2878, 1735, 1624, 1560, 1522, 1459, 1376, 1252, 1169, 1109, 1058, 987, 956, 901, 834, 771, 670 cm^{-1}; MS (ES) 704.2 ($M+H^+$).

4.19. 2′-*O*-Acetyl-3-decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (22)

According to general procedure 6.6 g of **17** (8.62 mmol) afforded **22** (6.3 g, 90%).

IR (KBr) 3545, 3448, 3393, 2972, 2940, 2882, 2831, 2787, 1727, 1638, 1586, 1522, 1490, 1460, 1382, 1335, 1309, 1298, 1247, 1201, 1166, 1100, 1057, 1036, 1006, 985, 947, 893, 864, 817, 756, 702, 669, 620 cm^{-1}; MS (ES) 806.16 ($M+H^+$).

4.20. 2′-*O*-Acetyl-3-decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (23)

According to general procedure 1.08 g of **19** (1.60 mmol) afforded **23** (0.68 g, 60%).

IR (KBr) 3431, 2974, 2937, 2876, 1734, 1629, 1524, 1459, 1376, 1243, 1167, 1083, 1058, 985, 957, 938, 904, 806, 671 cm^{-1}; MS (ES) 718.22 ($M+H^+$).

4.21. 2′-*O*-Acetyl-3-decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (24)

According to general procedure 0.12 g of **20** (0.15 mmol) afforded **24** (0.115 g, 93%).

IR (KBr) 3449, 2973, 2939, 1748, 1730, 1668, 1582, 1517, 1459, 1377, 1298, 1261, 1239, 1165, 1098, 1050, 985, 906, 866, 809, 764, 664, 622, 584, 544, 505, 483, 463, 444, 386 cm^{-1}; MS (ES) 820.19 ($M+H^+$).

4.22. 3,6-Hemiketals (25, 26) and 3-ketolides (derivatives 27, 28)

4.22.1. General procedure. To a solution of **21**–**24** in CH_2Cl_2 (c = 0.05 g/ml), DMSO (12 eq) and EDC × HCl (6 eq) were added. The reaction mixture was cooled to 15 °C and a solution of pyridinium trifluoroacetate (6 eq) in CH_2Cl_2 (c = 0.2 g/ml) was added dropwise during 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 CH_2Cl_2. Combined organic extracts were rinsed with brine, saturated aqueous $NaHCO_3$ solution, and water, dried over K_2CO_3, and evaporated yielding 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:MeOH:NH_4OH (90:3:0.3) as eluent to afford **25**–**28**.

4.23. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A 3,6-hemiketal (25)

According to general procedure 1.5 g of **21** (2.13 mmol) afforded **25** (0.313 g, 21%) as a white solid, mp 114–118 °C.

IR (KBr) 3373, 2968, 2936, 2877, 1728, 1716, 1615, 1526, 1520, 1456, 1384, 1261, 1181, 1099, 1031, 961, 864, 799, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (13-H), 4.21 (1′-H), 4.20 (9a-NCON′H), 3.96 (1″-H), 3.63 (11-H), 3.53 (5′-H), 3.78 (5-H), 3.26 (2′-H), 2.64 (2-H), 2.59 (10-H), 2.54 (3′-H), 2.32 (3′-N(CH_3)$_2$), 2.08 (4-H), 2.06 (8-H), 1.82 (14-Ha), 1.73 (4′-Ha), 1.62 (14-Hb), 1.48 (7-Ha), 1.39 (6-CH_3), 1.36 (7-Hb), 1.28 (10-CH_3), 1.27 (4′-Hb), 1.24 (5′-CH_3), 1.24 (4-CH_3), 1.15 (12-CH_3), 1.13 (1″-(CH_3)$_2$), 0.97 (8-CH_3), 0.96 (2-CH_3), 0.87 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4 (1-C), 157.4 (9a-NCONH), 103.7 (1′-C), 103.1 (3-C), 94.2 (5-C), 83.8 (6-C), 83.3 (11-C), 79.0 (13-C), 75.4 (12-C), 69.7 (5′-C), 69.6 (2′-C), 65.4 (3′-C), 49.2 (2-C), 48.3 (4-C), 46.5 (10-C), 42.6 (1″-C), 41.4 (7-C), 40.4 (3′-N(CH_3)$_2$), 29.0 (4′-C), 28.8 (8-C), 26.3 (6-CH_3), 23.6 (1″-(CH_3)$_2$), 21.6 (14-C), 21.2 (5′-CH_3), 21.2 (8-CH_3), 17.7 (12-CH_3), 14.3 (10-CH_3), 13.9 (2-CH_3), 12.9 (4-CH_3), 10.8 (15-CH_3); MS (ES) 660.6 ($M+H^+$); HRMS (ES) calcd for $C_{33}H_{61}N_3O_{10}$ ($M+H^+$) 660.4435, found 660.4395.

4.24. 3-Decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A 3,6-hemiketal (26)

According to general procedure 2.0 g of **22** (2.48 mmol) afforded **26** (0.516 g, 26%) as a white solid, mp 112–120 °C.

IR (KBr) 3448, 2974, 2938, 2877, 2782, 1720, 1667, 1580, 1512, 1460, 1384, 1324, 1299, 1231, 1195, 1115, 1099, 1072, 1049, 962, 862, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (6″-H), 7.32 (3″-H), 7.19 (5″-H), 4.91 (13-H), 4.36 (9a-NC0N′H), 4.21 (1′-H), 3.80 (5-H), 3.63 (11-H), 3.51 (5′-H), 3.23 (2′-H), 2.59 (10-H), 2.56 (2-H), 2.49 (3′-H), 2.27 (3′-N(CH_3)$_2$), 2.20 (8-H), 2.09 (4-H), 1.83 (14-Ha), 1.68 (4′-Ha), 1.62 (14-Hb), 1.55 (7-Ha), 1.47 (7-Hb), 1.42 (6-CH_3), 1.30 (2-CH_3), 1.26 (4′-Hb), 1.26 (5′-CH_3), 1.24 (4-CH_3), 1.21 (12-CH_3), 1.19 (10-CH_3), 1.07 (8-CH_3), 0.88 (15-CH_3);^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4 (1-C), 154.8 (9a-NCONH), 134.8 (1″-C), 128.3 (3″-C), 127.3 (5″-C), 127.1 (2″-C), 122.7 (4″-C), 121.9 (6″-C), 106.2 (1′-C), 103.3 (3-C), 94.2 (5-C), 83.6 (6-C), 83.3 (11-C), 79.0 (13-C), 75.6 (12-C), 69.7 (2′-C), 69.6 (5′-C), 65.5 (3′-C), 49.2 (2-C), 48.4 (4-C), 46.3 (10-C), 41.4 (7-C), 40.3 (3′N-(CH_3)$_2$), 28.6 (4′-C), 28.4 (8-C), 21.6 (14-C), 23.3 (5′-CH_3), 26.4 (6-CH_3), 21.5 (8-CH_3),17.7 (12- CH_3), 16.8 (12-CH_3), 14.2 (10-CH_3), 13.8 (2-CH_3), 12.9 (4-CH_3), 10.9 (15-CH_3); MS (ES) 762.12 ($M+H^+$); HRMS (ES) calcd for $C_{36}H_{57}Cl_2N_3O_{10}$ ($M+H^+$) 762.3499, found 762.3511.

4.25. 3-Keto-3-decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (27)

According to general procedure 0.18 g of **23** (0.25 mmol) afforded **27** (0.074 g, 41%) as a white solid, mp 114–119 °C.

IR (KBr) 3428, 2936, 1741, 1629, 1520, 1458, 1378, 1260, 1172, 1111, 1077, 1050, 985, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (13-H), 4.42 (1′-H), 4.34 (5-H), 3.91 (1″-H), 3.82 (2-H), 3.63 (5′-H), 3.21 (2′-H), 3.12 (4-H), 2.99 (6-OCH_3), 2.57 (3′-H), 2.33 (3′-N(CH_3)$_2$), 2.04 (8-H), 1.94 (14a-H), 1.75 (4′a-H), 1.54 (14 b-H), 1.38 (18-CH_3), 1.33 (16-CH_3), 1.26 (20-CH_3), 1.27 (5′-CH_3), 1.27 (4′b-H), 1.16 (1″-(CH_3)$_2$), 1.14 (21-CH_3), 1.27 (17-CH_3), 0.98 (19-CH_3), 0.90 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0 (3-C), 170.6 (1-C), 158.0 (9a-NCONH), 102.8 (1′-C), 75.8 (5-C), 79.4 (6-C), 74.4 (12-C), 74.2 (11-C), 70.3 (2′-C), 69.2 (5′-C), 65.8 (3′-C), 50.7 (2-C), 50.1 (6-OCH_3), 45.7 (4-C), 42.8 (1″-C), 40.4 (3′N-(CH_3)$_2$), 29.1 (4′-C), 27.4 (8-C), 23.8 (18-CH_3), 23.2 (1″-(CH_3)$_2$), 22.4 (14-C), 21.2 (5′-CH_3), 20.8 (19-CH_3), 16.8 (21-CH_3), 14.0 (16-CH_3), 13.2 (20-CH_3), 12.5 (17-CH_3), 11.3 (15-CH_3); MS (ES) 674.27 ($M+H^+$); HRMS (ES) calcd for $C_{34}H_{63}N_3O_{10}$ ($M+H^+$) 674.4592, found 674.4573.

4.26. 3-Keto-3-decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (28)

According to general procedure 0.73 g of **24** (0.89 mmol) afforded **28** (0.25 g, 34%) as a white solid, mp 109–119 °C.

IR (KBr) 3448, 2976, 2938, 2877, 2786, 1741, 1719, 1665, 1580, 1515, 1459, 1381, 1298, 1230, 1197, 1167, 1147, 1110, 1076, 1051, 986, 957, 937, 895, 859, 821, 761, 753, 622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (6″-H), 7.34 (3″-H), 7.18 (5″-H), 5.08 (13-H), 4.40 (1′-H), 4.31 (5-H), 3.81 (2-H), 3.62 (5′-H), 3.44 (6-OCH_3), 3.17 (4-H), 3.16 (2′-H), 2.75 (10-H), 2.49

(3′-H), 2.28 (3′-N(CH_3)$_2$), 2.19 (8-H), 1.94 (14a-H), 1.68 (4′a-H), 1.56 (14b-H), 1.32 (6-CH_3), 1.30 (2-CH_3), 1.27 (7a-H), 1.24 (10-CH_3), 1.23 (4′b-H), 1.23 (5′-CH_3), 1.19 (12-CH_3), 1.06 (4-CH_3), 1.03 (7b-H), 1.02 (8-CH_3), 0.91 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1 (3-C), 171.1 (1-C), 155.6 (9a-N<u>C</u>ONH), 135.1 (1″-C), 128.8 (3″-C), 128.2 (5″-C), 127.8 (2″-C), 123.1 (4″-C), 122.5 (6″-C), 103.1 (1′-C), 79.9 (6-C), 79.5 (13-C), 76.2 (5-C), 73.9 (12-C), 73.4 (11-C), 70.8 (2′-C), 69.7 (5′-C), 65.9 (3′-C), 51.1 (2-C), 50.9 (4-C), 50.6 (6-O-CH_3), 40.8 (3′N-(CH_3)$_2$), 39.0 (7-C), 29.3 (4′-H), 28.6 (8-C), 22.7 (14-C), 21.6 (5′-CH_3), 21.3 (19-CH_3), 17.2 (21-CH_3), 13.6 (16-CH_3), 12.8 (20-CH_3), 11.6 (15-CH_3), 7.6 (17-CH_3); MS (ES) 776.6 (M+H$^+$); HRMS (ES) calcd for $C_{37}H_{59}Cl_2N_3O_{10}$ (M+H$^+$) 776.3656, found 776.3638.

4.27. Mesylation of 3-OH (derivatives 29, 30, 33, 34)

4.27.1. General procedure. To a solution of **21**–**24** in pyridine (c = 0.02 g/ml), methylsulfonyl anhydride (3.5 eq) was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and residue dissolved in CH_2Cl_2. This solution was then rinsed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated yielding **29**, **30**, **33**, and **34**, respectively, that were used without further purification.

4.28. 2′-*O*-Acetyl-3-*O*-mesyl-3-decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (29)

According to general procedure 1.0 g of **21** (1.42 mmol) afforded **29** (0.87 g, 77%).

IR (KBr) 3422, 3065, 2972, 2876, 1735, 1637, 1618, 1535, 1487, 1459, 1377, 1330, 1240, 1206, 1193, 1059, 1004, 785, 773, 755, 682, 609 cm^{-1}; MS (ES) 783.2 (M+H$^+$).

4.29. 2′-*O*-Acetyl-3-*O*-mesyl-3-decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (30)

According to general procedure 1.5 g of **22** (1.86 mmol) afforded **30** (1.62 g, 97%).

IR (KBr) 3448, 3058, 2935, 1735, 1655, 1637, 1603, 1560, 1528, 1486, 1376, 1332,1240, 1208, 1193, 1097, 1059, 1001, 916, 822, 785, 773, 753, 681, 609 cm^{-1}; MS (ES) 884.05 (M+H$^+$).

4.30. 2′-*O*-Acetyl-3-*O*-mesyl-6-*O*-methyl-3-decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (33)

According to general procedure 0.35 g of **23** (0.49 mmol) afforded **33** (0.36 g, 92%).

IR (KBr) 3427, 2975, 2932, 2877, 2854, 1739, 1628, 1524, 1462, 1375, 1342, 1243, 1175, 1112, 1060, 958, 917, 830, 768, 707, 669 cm^{-1}; MS (ES) 796.28 (M+H$^+$).

4.31. 2′-*O*-Acetyl-3-*O*-mesyl-6-*O*-methyl-3-decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (34)

According to general procedure 1.50 g of **24** (1.86 mmol) afforded **34** (1.57 g, 94%).

IR (KBr) 3434, 3060, 2974, 2935, 1736, 1701, 1686, 1655, 1637, 1560, 1528, 1509, 1486, 1376, 1330, 1240, 1208, 1193, 1059, 785, 773, 753, 681, 609 cm^{-1}; MS (ES) 898.09 (M+H$^+$).

4.32. 3,6-Cyclic ethers (31, 32) and 2,3-anhydrolides (35, 36)

4.32.1. General procedure. To a solution of **29**, **30**, **33**, and **34** in DMF/THF (3.5:1, c = 0.02 g/ml), NaH (5 eq, 60% suspension in mineral oil) was added and the reaction mixture was stirred at 0 °C for 5 h, and additional 20 h at the room temperature. Into the reaction mixture saturated aqueous $NaHCO_3$ solution and ethyl acetate were added, and the layers were separated. The aqueous layer was extracted two more times with ethyl acetate. Combined organic extracts were rinsed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated yielding 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 crude product purified by chromatography on a silica gel column using CH_2Cl_2:MeOH:NH_4OH (90:3:0.3) as an eluent to afford **31**, **32**, **35,** and **36**, respectively.

4.33. 3-Decladinosyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A 3,6-cyclic ether (31)

According to general procedure 0.80 g of **29** (1.00 mmol) afforded **31** (0.17 g, 26%) as a white solid, mp 108–113 °C.

IR (KBr) 3428, 2972, 2938, 2876, 1735, 1619, 1528, 1459, 1383, 1330, 1270, 1179, 1144, 1073, 1051, 1030, 961, 893, 835, 799, 759, 635 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (13-H), 4.24 (1′-H), 4.20 (9a-NCON′<u>H</u>), 3.95 (1″-H), 3.83 (11-H), 3.64 (3-H), 3.55 (5′-H), 3.57 (5-H), 3.33 (2′-H), 3.25 (9-Ha), 2.92 (9-Hb), 2.76 (3′-H), 2.57 (2-H), 2.48 (3′-N(CH_3)$_2$), 2.06 (8-H), 2.04 (4-H), 1.92 (4′-Ha), 1.83 (14-Ha), 1.64 (14-Hb), 1.64 (7-Ha), 1.33 (4′-Hb), 1.29 (7-Hb), 1.28 (10-CH_3), 1.26 (5′-CH_3), 1.24 (4-CH_3), 1.23 (6-CH_3), 1.19 (2-CH_3), 1.14 (12-CH_3), 1.13 (1″-(CH_3)$_2$), 0.96 (8-CH_3), 0.88 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6 (1-C), 157.8 (9a-N<u>C</u>ONH), 103.9 (1′-C), 93.4 (5-C), 84.0 (6-C), 83.6 (3-C), 78.7 (13-C), 75.5 (12-C), 69.5 (2′-C), 69.4 (5′-C), 65.4 (3′-C), 46.5 (2-C), 45.7 (4-C), 42.6 (1″-C), 40.5 (3′-N(CH_3)$_2$), 40.3 (7-C), 30.1 (4′-C), 28.9 (8-C), 23.6 (1″-(CH_3)$_2$), 23.1 (6-CH_3), 21.7 (14-C), 21.3 (8-CH_3), 21.1 (5′-CH_3), 18.0 (12-CH_3), 18.0 (4-CH_3), 14.3 (2-CH_3), 12.8 (10-CH_3), 11.0 (15-CH_3); MS (ES) 644.2 (M+H$^+$); HRMS (ES) calcd for $C_{33}H_{61}N_3O_9$ (M+H$^+$) 644.4486, found 644.4472.

4.34. 3-Decladinosyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A 3,6-cyclic ether (32)

According to general procedure 1.50 g of **30** (1.69 mmol) afforded **32** (0.27 g, 21%) as a white solid, mp 88–95 °C.

IR (KBr) 3448, 2971, 2936, 2875, 2782, 1736, 1670, 1579, 1510, 1460, 1383, 1327, 1299, 1260, 1177, 1142, 1115, 1099, 1072, 1047, 961, 890, 861, 829, 763, 670, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (6″-H), 7.32 (3″-H), 7.18 (5″-H), 4.91 (13-H), 4.23 (9a-NC0N′H), 4.20 (1′-H), 3.88 (11-H), 3.56 (5-H), 3.51 (5′-H), 3.18 (2′-H), 2.59 (2-H), 2.52 (3′-H), 2.29 (3′-N(CH_3)$_2$), 2.18 (8-H), 2.06 (4-H), 1.84 (14-Ha), 1.71 (14-Hb), 1.69 (4′-Ha), 1.63 (7-Ha), 1.44 (4′-Hb), 1.28 (10-CH_3), 1.27 (7-Hb), 1.25 (6-CH_3), 1.23 (4-CH_3), 1.21 (5′-CH_3), 1.20 (2-CH_3), 1.13 (12-CH_3), 1.06 (8-CH_3), 0.89 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1 (1-C), 154.2 (9a-NCONH), 134.4 (1″-C), 127.6 (3″-C), 127.1 (5″-C), 126.4 (2″-C), 122.1 (4″-C), 121.2 (6″-C), 104.3 (1′-C), 93.4 (5-C), 83.3 (11-C), 83.2 (6-C), 82.8 (3-C), 79.1 (13-C), 74.9 (12-C), 69.1 (5′-C), 69.0 (2′-C), 64.9 (3′-C), 45.7 (2-C), 45.2 (4-C), 40.1 (7-C), 39.7 (3′N-(CH_3)$_2$), 30.0 (4′-C), 29.2 (8-C), 21.2 (14-C), 21.0 (5′-CH_3), 22.7 (6-CH_3), 20.9 (8-CH_3), 12.6 (4-CH_3), 17.0 (12-CH_3), 12.8 (10-CH_3), 13.7 (2-CH_3), 10.4 (15-CH_3); MS (ES) 746.02 ($M+H^+$); HRMS (ES) calcd for $C_{36}H_{57}Cl_2N_3O_9$ ($M+H^+$) 746.3550, found 746.3538.

4.35. 2,3-Anhydro-3-decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (35)

According to general procedure 0.5 g of **33** (0.62 mmol) afforded **35** (0.1 g, 20%) as a white solid, mp 100–105 °C.

IR (KBr) 3439, 2974, 2937, 1735, 1628, 1520, 1459, 1381, 1336, 1270, 1175, 1111, 1075, 1051, 958, 919, 832, 766, 535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (13-H), 4.93 (3-H), 4.56 (1′-H), 3.90 (1″-H), 3.23 (5-H), 3.53 (5′-H), 3.27 (2′-H), 3.12 (6-OCH_3), 2.70 (3′-H), 2.36 (3′-N(CH_3)$_2$), 1.52 (4-H), 1.91 (14a-H), 2.05 (8-H), 1.70 (4′a-H), 1.49 (14b-H), 1.36 (18-CH_3), 1.30 (16-CH_3), 1.25 (20-CH_3), 1.25 (5′-CH_3), 1.25 (4′b-H), 1.15 (1″-(CH_3)$_2$), 1.12 (21-CH_3), 1.06 (17-CH_3), 0.96 (19-CH_3), 0.88 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (1-C), 158.1 (9a-NCONH), 146.4 (2-C), 127.4 (3-C), 106.7 (1′-C), 86.1 (5-C), 79.5 (6-C), 74.2 (11-C), 75.0 (12-C), 70.7 (2′-C), 68.3 (5′-C), 65.9 (3′-C), 50.7 (6-OCH_3), 42.8 (1″-C), 39.0 (3′N-(CH_3)$_2$), 40.4 (4-C), 29.1 (4′-C), 28.4 (8-C), 23.4 (18-CH_3), 22.3 (14-C), 22.1 (1″-(CH_3)$_2$), 20.9 (5′-CH_3), 20.5 (19-CH_3), 16.8 (21-CH_3), 14.2 (16-CH_3), 12.5 (20-CH_3), 11.4 (15-CH_3), 8.8 (17-CH_3); MS (ES) 658.22 ($M+H^+$); HRMS (ES) calcd for $C_{34}H_{63}N_3O_9$ ($M+H^+$) 658.4642, found 658.4654.

4.36. 2,3-Anhydro-3-decladinosyl-6-*O*-methyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (36)

According to general procedure 1.00 g of **34** (1.11 mmol) afforded **36** (0.024 g, 2.8%) as a white solid, mp 94–99 °C.

IR (KBr) 3452, 2981, 2941, 1748, 1731, 1662, 1582, 1516, 1459, 137, 1298, 1261, 1243, 1165, 1098, 1052, 985, 906, 867, 810, 764, 666, 625, 587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (6″-H), 7.34 (3″-H), 7.18 (5″-H), 5.16 (13-H), 4.92 (3-H), 4.39 (1′-H), 3.20 (5-H), 3.52 (5′-H), 3.30 (6-OCH_3), 3.18 (2′-H), 2.61 (10-H), 2.50 (3′-H), 2.27 (3′-N(CH_3)$_2$), 2.04 (8-H), 1.93 (14a-H), 1.68 (4′a-H), 1.55 (4-H), 1.52 (14b-H), 1.35 (6-CH_3), 1.29 (2-CH_3), 1.26 (4′b-H), 1.25 (10-CH_3), 1.25 (5′-CH_3), 1.13 (12-CH_3), 1.04 (4-CH_3), 0.97 (8-CH_3), 0.89 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3 (1-C), 156.0 (9a-NCONH), 146.8 (2-C), 127.7 (3-C), 134.8 (1″-C), 128.3 (3″-C), 127.5 (5″-C), 127.0 (2″-C), 122.8 (4″-C), 122.1 (6″-C), 106.9 (1′-C), 86.3 (5-C), 79.1 (6-C), 76.1 (13-C), 73.4 (11-C), 73.5 (12-C), 70.7 (2′-C), 69.9 (5′-C), 65.7 (3′-C), 50.0 (6-O-CH_3), 40.3 (3′N-(CH_3)$_2$), 40.7 (4-C), 35.4 (7-C), 28.3 (4′-H), 28.2 (8-C), 22.4 (14-C), 21.3 (5′-CH_3), 20.6 (8-CH_3), 16.9 (21-CH_3), 14.2 (2-CH_3), 12.8 (20-CH_3), 11.4 (15-CH_3), 7.6 (4-CH_3); MS (ES) 760.70 ($M+H^+$); HRMS (ES) calcd for $C_{37}H_{59}Cl_2N_3O_9$ ($M+H^+$) 760.3707, found 760.3677.

4.37. 3-Decladinosyl-3-*O*-(4-nitrophenyl)acyl-9-deoxo-9-dihydro-9a-(*N*′-isopropylcarbamoyl)-9a-aza-9a-homoerythromycin A (37)

To a solution of 4-nitrophenylacetic acid (0.85 g, 1.81 mmol) in dry CH_2Cl_2 (25 ml), TEA (0.65 ml, 4.68 mmol) was added and the reaction mixture was cooled to 5 °C. Pivaloyl chloride (0.57 ml, 4.68 mmol) was then added and the reaction mixture stirred for 30 min. To the reaction mixture pyridine (1.27 ml, 15.70 mmol) and the solution of **21** (1.00 g, 1.42 mmol) in dry CH_2Cl_2 (5 ml) were added and the reaction mixture stirred at room temperature for 20 h. Saturated aqueous $NaHCO_3$ solution (30 ml) was added and the layers were separated. The aqueous layer was extracted two more times with CH_2Cl_2. Combined organic extracts were rinsed with brine, dried over K_2CO_3, and evaporated yielding 1.43 g of oily product which was dissolved in MeOH (50 ml) and stirred for 24 h at room temperature. The solvent was evaporated and the crude product purified by chromatography on a silica gel column using CH_2Cl_2:MeOH:NH_4OH (90:3:0.3) as an eluent to afford **37** (0.45 g, 38%) as a white solid, mp 112–120 °C.

IR (KBr) 3449, 2975, 2939, 2877, 2791, 1741, 1626, 1604, 1523, 1459, 1382, 1347, 1255, 1167, 1111, 1075, 1051, 1032, 984, 959, 856, 767, 728, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (4‴-H, 6‴-H), 7,54 (3‴-H, 7‴-H), 5.43 (3-H), 5.06 (13-H), 4.42 (9a-NCON′H), 4.23 (1′-H), 3.92 (1‴-H), 3.60 (5-H), 3.49 (5′-H), 3.26 (2′-H), 2.68 (2-H), 2.45 (3′-H), 2.29 (3′-N(CH_3)$_2$), 2.20 (8-H), 1.95 (14-Ha), 1.90 (4-H), 1.66 (4′-Ha), 1.50 (14-Hb), 1.32 (6-CH_3), 1.26 (4′-Hb), 1.29 (10-CH_3), 1.22 (5′-CH_3), 1.17 (12-CH_3), 1.05 (4-CH_3), 0.95 (2-CH_3), 1.15 (1″-(CH_3)$_2$), 1.08 (8-CH_3), 0.87 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (1-C), 169.9 (1″-CO), 158.7 (9a-NCONH), 147.1 (5‴-C), 141.5 (2‴-C), 130.5 (3‴-C, 7‴-C), 123.6 (2‴-C, 6‴-C), 103.4 (1′-C), 88.3 (5-C), 78.1 (13-C), 74.5 (3-C), 74.2 (6-C), 70.4 (2′-C), 69.8 (5′-C), 65.4 (3′-C), 44.6 (2-C),

41.3 (1‴-C), 38.4 (4-C), 48.7 (1″-C), 41.3 (7-C), 40.2 (3′-N(CH_3)$_2$), 28.7 (4′-C), 27.8 (8-C), 27.4 (6-CH_3), 23.2 (1″-(CH_3)$_2$), 21.7 (14-C), 20.7 (8-CH_3), 20.8 (5′-CH_3), 16.9 (12-CH_3), 15.2 (2-CH_3), 12.5 (10-CH_3), 11.0 (15-CH_3), 8.9 (4-CH_3); MS (ES) 825 (M+H^+); HRMS (ES) calcd for $C_{41}H_{68}N_4O_{13}$ (M+H^+) 825.4861, found 825.4847.

4.38. 3-Decladinosyl-3-*O*-(4-nitrophenyl)acyl-9-deoxo-9-dihydro-9a-[*N*′-(2,4-dichlorphenyl)carbamoyl]-9a-aza-9a-homoerythromycin A (38)

To a solution of 4-nitrophenylacetic acid (0.74 g, 4.09 mmol) in dry CH_2Cl_2 (25 ml), TEA (0.57 ml, 4.09 mmol) was added and the reaction mixture was cooled to 5 °C. Pivaloyl chloride (0.50 ml, 4.09 mmol) was then added and the reaction mixture stirred for 30 min. To the reaction mixture pyridine (1.1 ml, 13.60 mmol) and the solution of **22** (1.00 g, 1.23 mmol) in dry CH_2Cl_2 (5 ml) were added, and the reaction mixture stirred at room temperature for 20 h. Saturated aqueous $NaHCO_3$ solution (30 ml) was added and the layers were separated. The aqueous layer was extracted two more times with CH_2Cl_2. Combined organic extracts were rinsed with brine, dried over K_2CO_3, and evaporated yielding 1.14 g of oily product which was dissolved in MeOH (50 ml) and stirred for 24 h at room temperature. The solvent was evaporated and the crude product purified by chromatography on a silica gel column using CH_2Cl_2:MeOH:NH_4OH (90:3:0.3) as an eluent to afford **38** (0.52 g, 45%) as a white solid, mp 118–125 °C.

IR (KBr) 3448, 2975, 2938, 2879, 2789, 1741, 1665, 1607, 1578, 1522, 1459, 1382, 1347, 1298, 1256, 1229, 1165, 1110, 1074, 1050, 983, 958, 857, 821, 731, 685, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (4‴-H, 6‴-H), 8.13 (6″-H), 7.51 (3‴-H, 7‴-H), 7,32 (3″-H), 7.18 (5″-H), 5.36 (3-H), 5.03 (13-H), 4.42 (9a-NCON′H), 4.23 (1′-H), 3.80 (1‴-H), 3.69 (5-H), 3.49 (5′-H), 3.25 (2′-H), 2.68 (2-H), 2.45 (3′-H), 2.32 (3′-N(CH_3)$_2$), 2.29 (8-H), 1.92 (14-Ha), 1.92 (4-H), 1.66 (4′-Ha), 1.58 (7-Ha), 1.51 (14-Hb), 1.38 (10-CH_3), 1.32 (6-CH_3), 1.26 (7-Hb), 1.18 (4′-Hb), 1.24 (12-CH_3), 1.16 (5′-CH_3), 1.07 (8-CH_3), 0.95 (2-CH_3), 0.94 (4-CH_3), 0.85 (15-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (1-C), 169.9 (1″-CO), 154.9 (9a-NCONH), 147.2 (5‴-C), 141,3 (2‴-C), 134.8 (1″-C), 130.6 (3‴-C, 7‴-C), 128.5 (3″-C), 127.4 (2″-C, 5″-C), 123.7 (2‴-C, 6‴-C), 122.6 (4″-C), 122.2 (6″-C), 103.9 (1′-C), 88.3 (5-C), 77.6 (13-C), 74.3 (3-C), 74.2 (6-C), 70.5 (2′-C), 69.8 (5′-C), 65.5 (3′-C), 47.3 (4-C), 44.6 (2-C), 41.2 (1‴-C), 41.2 (7-C), 40.5 (3′-N(CH_3)$_2$), 29.1 (4′-C), 27.5 (8-C), 27.4 (6-CH_3), 22.0 (14-C), 21.1 (5′-CH_3), 21.0 (8-CH_3), 12.3 (12-CH_3), 13.1 (10-CH_3), 11.2 (15-CH_3), 3.2 (4-CH_3); MS (ES) 927.2 (M+H^+); HRMS (ES) calcd for $C_{44}H_{64}Cl_2N_4O_{13}$ (M+H^+) 927.3925, found 927.3921.

4.39. Antibacterial activity

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

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