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Synthesis and activity of new macrolones: Conjugates between 6(7)-(2′-aminoethyl)-amino-1-cyclopropyl-3-carboxylic acid (2′-hydroxyethyl) amides and 4″-propenoyl-azithromycin

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ABSTRACT

A set of novel macrolones containing the flexible C8 basic linker and quinolone 3-(2′-hydroxyethyl)carboxamido group has been prepared and structurally characterized by NMR and IR spectroscopy, mass spectrometry and molecular modeling. The new compounds were evaluated in vitro against a panel of erythromycin-susceptible and erythromycin-resistant Gram-positive and Gram-negative bacterial strains. Compared to azithromycin, most of the compounds exhibited improved in vitro potency against the key respiratory pathogens.

1. Introduction

Concept of combining active macrolide scaffold and (hetero)-aromatic unit via flexible linker resulted with compounds showing remarkable antibacterial activity, ketolide derivatives telithromycin and its congeners in particular.[1,2] The secret behind the success of telithromycin is the aryl-alkyl arm attached to a carbamate heterocycle that involves the C(11) and C(12) positions of the ketolide macrocycle. Interactions of this moiety with ribosome's A752Ec-U2609Ec base pair, actually representing a second binding site, increase the affinity of the ketolide scaffold for the ribosome by several hundred-fold.[3] In the case of macrolones similar concept is used as the derivative of quinolone is attached to macrolide scaffold via flexible linker.[4–8]

Due to flexibility of their structure, the macrolones are good candidates for possible multiple interactions with the ribosome. Macrolide part of the macrolone should have a major role in this binding. For macrolide antibiotics, beside one hydrogen bond formed between the 2′-OH group of desosamine sugar and nucleotide 2058Ec (*Escherichia coli* numbering),[3,9–11] tight surrounding by rRNA and abundance of hydrophobic interactions are invoked to explain their affinity of macrolides towards ribosome ($K_d \approx 10^{-8}$ M).[12] Exactly how and where the quinolone part of the molecule binds, however, is still unclear.

It is well known that basicity and lipophilicity are the key properties influencing ADME properties as well as activity of molecules in drug-discovery process.[13] In this respect, conjugate molecules containing two nitrogen atoms in the linker between standard macrolide antibiotics (erythromycin, clarithromycin, and azithromycin) and derivatives of quinolone 3-carboxylic acid were prepared, in order to modulate basicity and investigate effect on biological activity.[8] Furthermore, to remove liabilities of carboxylic groups and improve ADME properties but still retain good antibacterial activity, carboxylic group at quinolone position C(3) was transformed into 2-hydroxyethylamide unit.

Herein, we describe the synthesis and report on some properties of a short series of macrolones, prepared following above concepts as a guideline.

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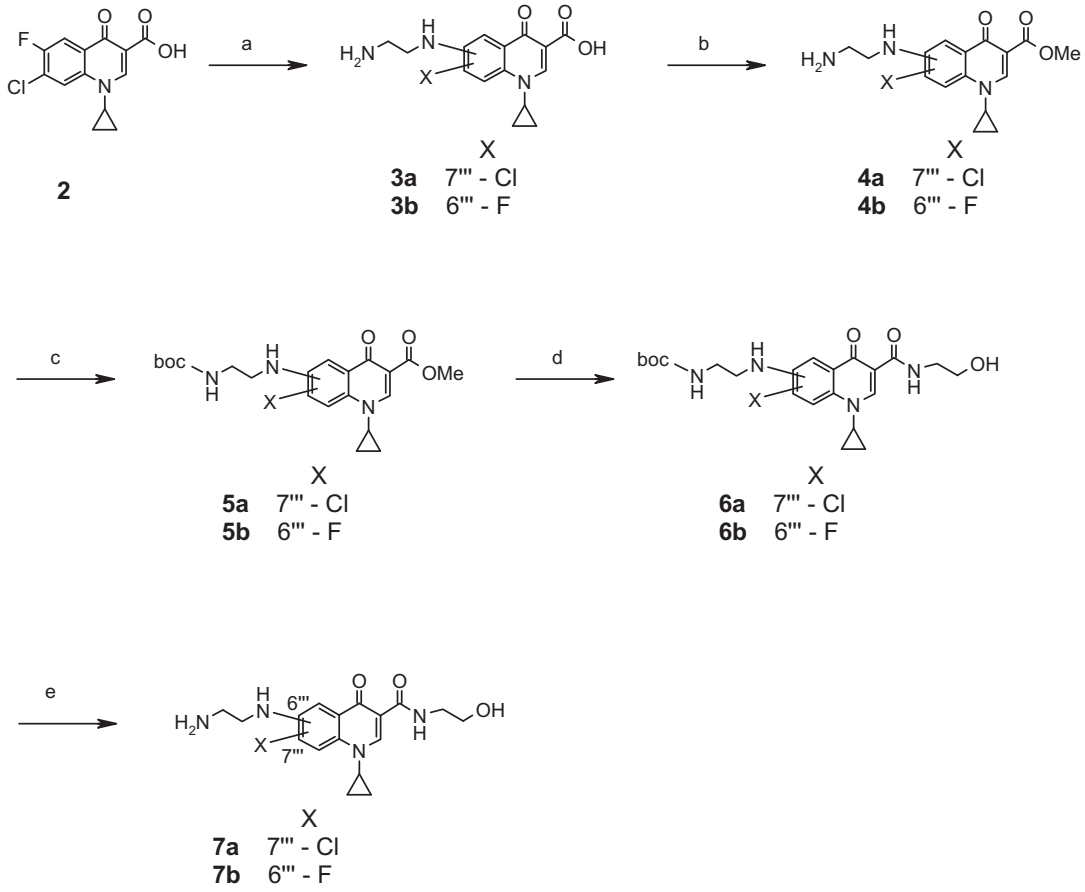
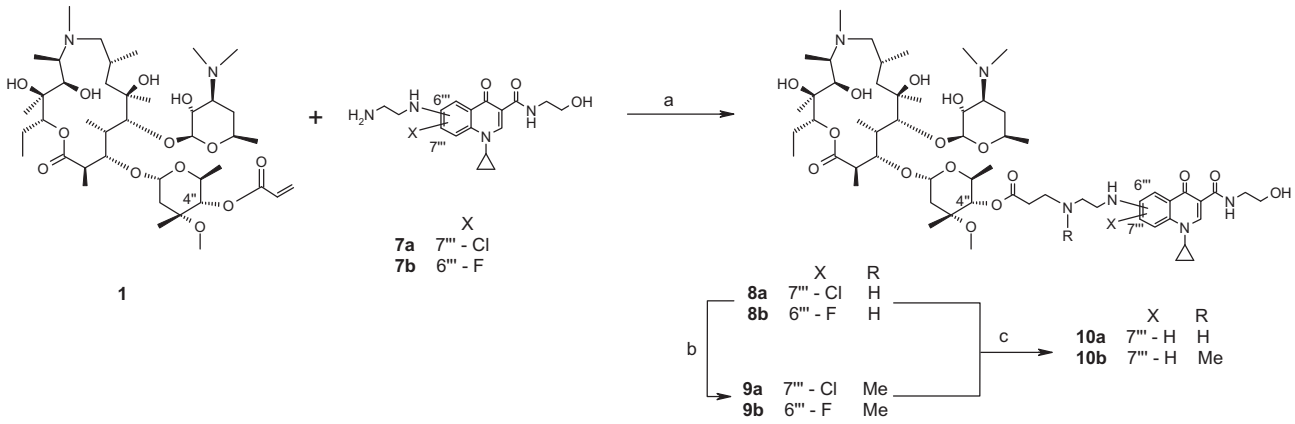


Scheme 1. Chemical pathway for synthesis of quinolone subunits **7a** and **7b**. Reagents and conditions: (a) **2**, 1,2-diaminoethane, *N*,*N*-dimethylacetamide, 120 °C, 8 h, rt, 2 h, 0 °C, 1 h; 6% HCl, charcoal, 85 °C, 1 h; 35–40 °C; 4 °C, overnight; (b) **3a** or **3b**, 3% HCl in MeOH, 70 °C, 24 h; (c) **4a** or **4b**, di-*tert*-butyl dicarbonate, dioxane/H2O (2:1), 1 M NaOH, 0 °C to rt, 1 h; (d) **5a** or **5b**, 2-aminoethanol, MeOH, 75 °C, 12 h; (e) **6a** or **6b**, CF_3COOH, DCM, rt, 1 h.



Scheme 2. Chemical pathway for synthesis of macrolones **8a**, **8b**, **9a**, **9b**, **10a**, **10b**. Reagents and conditions: (a) **1**, **7a** or **7b**, MeCN, H_2O, Et_3N, 80 °C, 12 h; (b) **8a** or **8b**, 36% of HCHO/HCOOH, CH_3Cl, rt, 12 h, 30 °C for 8 h, (c) **8a** or **9a**, 10% Pd/C, MeOH, rt, H_2, (5 bar), 24 h.

2. Results and discussion

2.1. Chemistry

Target compounds **8a** and **8b** were prepared according to the Scheme 2 by Michael addition of 6- or 7-β-aminoethylamino derivatives **7a** and **7b**, prepared according to the Scheme 1, on 4″-propenoyl azithromycin (**1**).[14]

Preparation of β-aminoethyl amides **7a**, **7b** required proper sequence of the reactions; first aminolysis of the halogen atoms in the quinolonic acid **2** by 1,2-diaminoethane, then separation of the two products **3a**, **3b**, followed by esterification to **4a**, **4b**, protection of terminal β-amino group to give **5a**, **5b** and final amidolysis of the ester group to amides **6a**, **6b**. Deprotection of **6a** and **6b** afforded **7a** and **7b**, which were purified and used as the quinolone building blocks.

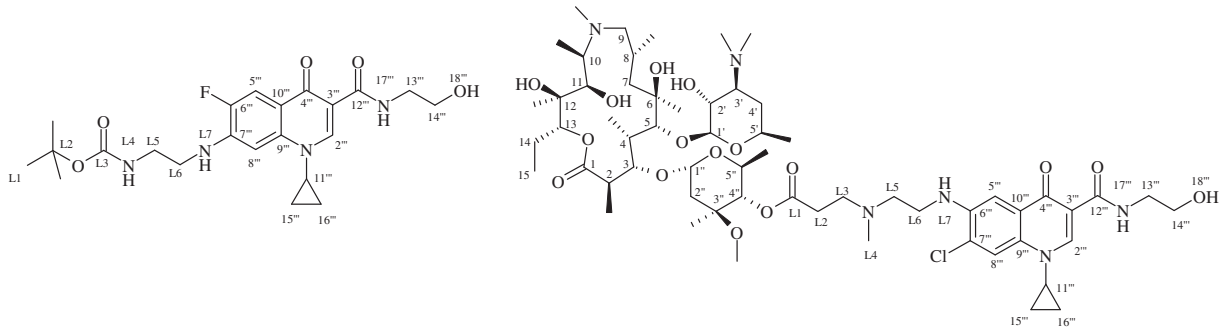


Figure 1. Examples of structures and atom numbering used for NMR assignment.

In the Scheme 2 preparation of the set of target structures **8a**, **8b**, **9a**, **9b**, **10a** and **10b** is outlined. Michael addition on macrolide acrylic ester derivative **1** proved sensitive to the reaction conditions. When this reaction was attempted with the excess of **7a** or **7b** (2.2 equiv) in the presence of aqueous acetonitrile (10% of water) and DBU as basic catalyst, desired products **8a** and **8b** were not obtained after 24 h stirring at room temperature. When reaction proceeded in aqueous acetonitrile (8% of water) with excess of **7a** or **7b** (2.2 equiv) and Et_3N as basic catalyst at 80 °C for 24 h, the yields up to ca. 70% were achieved. Only ca. 30% conversion was observed after 12 h under the same conditions. *tert*-Amine derivatives **9a** and **9b** were prepared in 60–70% yield by reductive formylation with HCHO/HCOOH in chloroform at 30 °C for 2 h. Dechloro derivatives **10a** and **10b** were prepared by catalytical hydrogenolysis in the presence of Pd/C, under H_2 at 5 Barr for 20 h in 30–50% yields.

Since quinolone 3-carboxylic amide unit was tethered to the macrolide skeleton through rather flexible linker, it allowed the quinolone moiety to occupy different spatial positions. The inherent flexibility could result in different fitting modes on the rRNA subunits, allowing formation of the hydrogen bonds with specific H-donors and H-acceptors. In view of the importance of the macrolactone ring for the proper positioning of macrolides, conformational flexibility of the linker-quinolone subunit involved in the interactions with the ribosome possibly matches flexibility of the rRNA interacting region with macrolides.[15,16]

As already mentioned, basicity of targeted compounds contributes usually to their efficacy. On the other hand, it is known that basic nitrogen inserted into the lactone ring does not contribute to the binding of azithromycin.[15] It is obvious that the two *tert*-amino groups and two *sec*-amino groups in **8a** and **8b** confer strong basicity to these macrolones, and even more so the three *tert*-amino groups to the macrolones **9a**, **9b** and **10b**. Dimethylamino group of the desosamine sugar exists at physiological pH up to 96–98% in the protonated form, which interacts in the pH-dependent manner with the backbone oxygens of rRNA. Additional interactions of this type can be expected for strongly basic amino groups offered by novel macrolones **8**–**10**.

2.2. Structural studies

The structures of all synthesized compounds were determined by mass spectrometry, as well as IR and NMR spectroscopies. Mass measurement accuracy, as experimentally determined, was within the specified limit for the instrument used (better than ±5 ppm). The mass spectra for new compounds were in agreement with the proposed structure.

2.2.1. NMR analysis

MS results were further confirmed by the NMR spectra, which revealed two sets of signals arising from azithromycin and quinolone moieties, as well as signals reflecting the number of methylene groups in the linker. Atom numbering of quinolone and macrolone derivatives is shown at Figure 1.

The newly formed ester carbonyl carbon resonates in the ^{13}C NMR spectrum around 172 ppm. The significant deshielding of the H4″ signal in the proton spectrum, together with its long-range coupling to the new carbonyl signal in HMBC spectrum provided evidence that the esterification occurred at 4″-OH group of the macrolide scaffold.

In the ^1H and ^{13}C NMR spectra of the compounds (**8b** and **9b**) were visible additional couplings between fluorine substituent attached at C6 and the neighboring atoms of the quinolone moiety. For example, the coupling constants $J_{F\text{-}H}$ and $J_{F\text{-}C}$ for the compound **8b** were as follows: $^3J_{F\text{-}H}$ = 12 Hz, $^4J_{F\text{-}H}$ = 7 Hz, $^1J_{F\text{-}C}$ = 244 Hz, $^2J_{F\text{-}C}$ = 19 and 14 Hz and $^3J_{F\text{-}C}$ = 6 Hz which are consistent with literature data on similar compounds.[17]

During comparison of ^1H NMR spectra of compounds containing de-chloroquinolone unit **10a** and **10b** with their chloro analogues **8a** and **9a** it was observed that they have an additional aromatic proton signal.

Structural features of compounds influence the strength of their binding to ribosome and, consequently, their antibacterial activity (MIC values). In order to gain more information on structural properties of prepared macrolone compounds we carried out the conformational analysis on compounds **9a** and **10b** using NMR and molecular modelling techniques. NMR data were used to constrain searching of conformational space around the macrolone flexible linker, but also to ascertain the conformation of the macrocycle.

Previous conformational studies on macrolides, erythromycin and azithromycin,[14,18–20] have established that the macrocycle can adopt two types of conformations (folded-in and folded-out) distinguished by the outward or inward folding of the C3 to C5 region. Folded-in conformers have characteristic torsion angle between H2 and H3 yielding a small coupling constant ($^3J_{H2,H3} \approx$ 2–3 Hz) and exhibit close proximity of protons H3 and H11, resulting in strong NOE crosspeak in NOESY spectrum. Alternatively, folded-out conformers, in addition to a large $^3J_{H2,H3}$ value (≈10 Hz) exhibit an NOE interaction between protons H4 and H11. In addition, a new type of macrocycle conformation termed as 3-*endo*-folded out was described[21] as conformation intermediate between classical folded-out and folded-in structure characterized by the presence of both H3/H11 and H4/H11, as well as the absence of H3/H8 and H8/H11 NOE crosspeaks.

Coupling constants $^3J_{H2,H3}$ in both **9a** and **10b** have the value of 4 Hz. Their NOESY spectra display both H3/H11 and H4/H11, but no H3/H8 and H8/H11 NOE crosspeaks which establishes that macrocycles of these compounds adopt 3-*endo*-folded conformation in DMSO-d_6, similar to the solution structure of azithromycin. This leads to conclusion that the addition of the linker with quinolone moiety attached to cladinose sugar does not change the azithromycin-like conformation of the macrocycle.

Analysis of observed intra-sugar NOE's and coupling constants showed that the both sugar moieties adopt the usual Everett–Tyler chair conformation,[14] while the NOE contacts between sugar moieties (like H1′/H5″ and H1′/H3″OMe) suggest up-up orientation of the alpha faces of the two sugars. Furthermore, H1′/H5 and H1′/H4Me NOE's confirm the perpendicular orientation of the desosamine, while H-1′/H-5″ and H-5/H-5″ indicate an approximately parallel orientation of the cladinose sugar with respect to the macrocycle.

Linker and the quinolone moiety protons show no conclusive NOE cross peaks neither with macrocycle or the sugars for both **9a** and **10b**, suggesting that the attached quinolone is most probably freely rotating away from the rest of the molecule.

2.2.2. Computational analysis

Stochastic conformational search around the flexible amino linker using NMR constrains has been performed for compound **10b**. Macrolactone and desosamine rings were not optimized as the available force fields do not reproduce reliably macrolactone conformations and relative sugar orientations. Crystal structure of azithromycin was used as a template.[22] Analysis of NOE cross peaks in the NOESY spectrum indicated that there is no strong interaction between linker protons and the quinolone moiety with the rest of the molecule. This high conformational flexibility enables 'quinolone' arm to be stretched out in the space also enabling new interactions within the ribosome binding site.

Superposed X-ray structure conformations for azithromycin,[9,15] telithromycin,[9,23] ABT-773[22] and the lowest conformation for compound **10b** are shown in Figure 2. It is interesting to notice that substituents at different positions on macrolactone ring have different spatial arrangements and therefore different interactions with ribosome. Until now there is a number of evidence including here mentioned ketolides that high structural diversity is tolerated within the flexible macrolide-binding site of ribosome. In spite of the knowledge gained on macrolide binding so far,[3,9,11,15,21–23] an understanding of the mode of their interactions with ribosome still remains incomplete with many issues unresolved. Therefore, it can only be speculated about the possible binding mode of the compound **9a** and **10b** but it is likely that the additional interaction involving quinolone moiety might lead to the further stabilization of a complex with ribosome which could be reason of their improved antibacterial activity. In Figure 3, twenty most stable conformations of compound **10b** are shown. Since energy difference between first ten conformations is only several kcal/mol (3 kcal/mol at MMFF94x as well as at the B3LYP/6-31G** level), any of these conformations can be adopted depending on the entropic and enthalpic effect within the ribosome binding site.

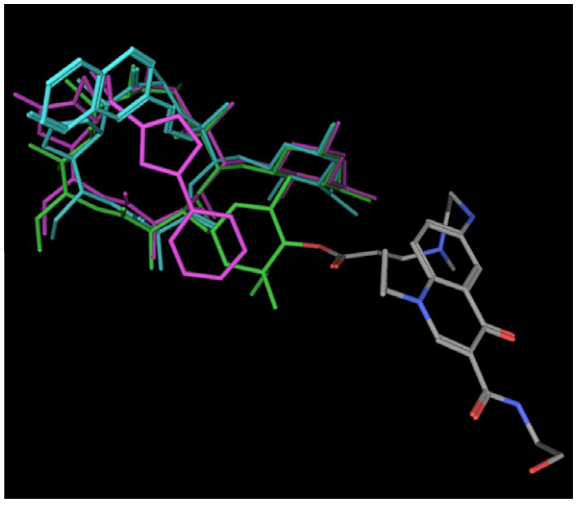


Figure 2. Superposed X-ray structure conformations for azithromycin (green), ABT-773 (cyan), telithromycin (magenta) and most stable conformation for compound **10b** (atom color).

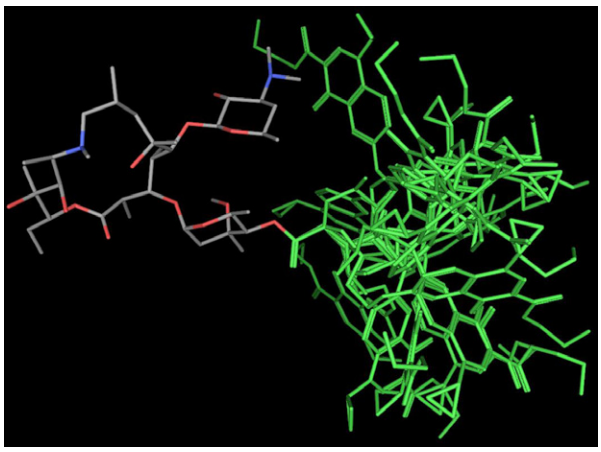


Figure 3. First twenty most stable conformations of **10b** satisfying NMR constrains.

2.3. Antimicrobial activity

Biological properties of target compounds **8a**, **8b**, **9a**, **9b**, **10a**, **10b** and phenotypes of tested pathogens are shown in Table 1. For all compounds antibacterial activity was determined by a standard broth microdilution method according to CLSI guidelines,[24,25] with azithromycin as standard for comparison. The results shown are expressed as minimum inhibitory concentrations (MICs) in units of μg/mL. Both relevant Gram-positive (*Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus*) and Gram-negative (*Haemophilus influenzae* and *Moraxella catarrhalis*) respiratory tract pathogens that were either sensitive or resistant to macrolide antibiotics were tested. Macrolide resistance was due to two major mechanisms—production of efflux pumps (M), or ribosome modification by methylation. Methylase expression was inducible (*i*MLS_b) or constitutive (*c*MLS_b).

The quinolone intermediates **5a**, **5b–7a** and **7b** proved to be antibacterially inactive. However, when linked to azithromycin scaffold, compounds showed potency against Gram-positive pathogens exceeding that of azithromycin *per se*. Compounds containing chlorine at the position 7 of quinolone moiety (**8a** and **9a**) showed better antibacterial activity compared to their de-halogenated counterparts (**10a** and **10b**) and molecules linked at the position 7 (having fluorine atom at the position 6 of quinolone—**8b** and **9b**). Methylation of central nitrogen atom in the linker resulted in additional improvements of potency against erythromycin resistant strains, with either *i*MLS_b or M phenotype. The most potent compound overall was **9a** with MIC of 0.5 and 2 μg/mL against efflux resistant *S. pneumoniae* and *S. pyogenes*, and MIC of 4 and 2 μg/mL against *S. pneumoniae* and *S. pyogenes* strains with inducibly expressed *erm*(B) gene, respectively. Conversely, when compared to azithromycin potency against Gram-negative bacteria *H. influenzae* and *M. catarrahlis* is diminished. In contrast to inducible, constitutive expression of methyltransferase could not be overcome by tested compounds.

3. Conclusion

Following the successful concept of telithromycin as the compound utilizing the idea of linking two structurally different moieties via flexible linker and thus creating two separate sites for

Table 1
In vitro antibacterial activity of selected compounds given as minimum inhibitory concentration (MIC) in units of μg/mL

Organism	*S. aureus*	*S. pneumoniae*	*S. pyogenes*	*S. aureus*	*S. pneumoniae*	*S. pyogenes*	*S. aureus*	*S. pneumoniae*	*S. pyogenes*	*S. pneumoniae*	*S. pyogenes*	*S. aureus*	*H. influenzae*	*M. catarrhalis*
	ATCC13709	SP 030	3565	PK1	Ci137	Finland 2	90265/97	134 GR-M	Finland 11	58 Spain	166 GR-Micro	PK2	ATTC 49247	ATCC 23246
Compound	eryS	eryS	eryS	M	M	M	iMLSb	iMcLSb	iMLSb	cMLSb	cMLSb	cMLSb		
5a	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5b	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	8
6a	>64	16	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	32
6b	64	16	16	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	16
7a	>64	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	64
7b	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
8a	4	⩽0.125	⩽0.125	>64	2	4	>64	32	1	16	32	>64	4	0.5
8b	4	⩽0.125	⩽0.125	>64	4	16	>64	64	4	32	>64	>64	4	0.5
9a	2	⩽0.125	⩽0.125	32	0.5	2	>64	4	2	32	>64	>64	4	1
9b	16	⩽0.125	0.5	>64	2	16	>64	16	16	>64	>64	>64	16	8
10a	4	⩽0.125	0.25	>64	4	16	>64	32	4	>64	>64	>64	8	0.5
10b	2	⩽0.125	0.25	64	1	4	>64	4	4	>64	>64	>64	4	1
AZM	0.5	⩽0.125	⩽0.125	>64	8	8	>64	>64	16	>64	>64	>64	1	⩽0.125

AZM = azithromycin; eryS = erythromycin sensitive; iMLSb = inducible resistance to macrolide, licosamide and streptogramin (MLSb) antibiotics; iMcLSb = inducible resistance to macrolide and constitutive resistance to lincosamide antibiotics; cMLSb = constitutive MLSb resistance; M = efflux mediated macrolide resistance.

interaction with the ribosome, macrolone compounds **8a**, **8b**, **9a**, **9b**, **10a** and **10b** were synthesized. Structural studies (NMR and molecular modeling) revealed that studied compounds exhibit high conformational flexibility that enables quinolone 'arm' to be stretched out in the space possibly enabling new interactions within the ribosome binding site. This hypothesis was supported by antibacterial potency of synthesized conjugate compounds against Gram-positive pathogens exceeding that of macrolide (azithromycin) alone. It is important to note that the quinolone parts did not have any antibacterial properties before linking to azithromycin scaffold. It is likely that the additional interaction involving quinolone moiety leads to the further stabilization of a complex with the ribosome which could be a reason of their improved antibacterial activity.

The introduction of nitrogen atoms and, thus, increased basicity, proved to be detrimental for antibacterial activity. However, tertiary nitrogen in the linker (in comparison to secondary) seems to be advantageous against erythromycin resistant strains. It would be interesting to see what effect a longer alkyl chains attached to this nitrogen would have on the antibacterial activity.

4. Experimental

4.1. General methods

All commercial reagents (Merck, Sigma-Aldrich) were used as provided unless otherwise indicated, and all solvents are of the highest purity unless otherwise noted. Starting 4″-*O*-propenoyl-azithromycin (**1**) was prepared as described,[26] and 6-fluor-7-chloro-quinoline 3-carboxylic acid (**2**) was commercially available.

ES (Electrospray) mass spectra were recorded on instruments Platform LCZ (Micromass, UK) and LCQ Deca (Finnigan, USA).

IR spectra were recorded on Nicolet Magna 760 FTIR instrument with KBr optic in 600–4000 cm^{-1} range with 32 scans and resolution 4 cm^{-1} as KBr pellets.

Reaction progress and products purity were followed by TLC on Merck plate (Darmstadt, DE) using systems of solvents as follow: DCM/MeOH/NH_4OH (90:9:0.5), DCM/MeOH/NH_4OH (90:5:0.5) and DCM/MeOH/NH_4OH (90:15:1.5).

4.2. Biology

For all newly synthesized compounds antibacterial activity was determined by a standard broth microdilution method according to CLSI guidelines,[24] except that for *Streptococcus* medium lysed blood was substituted with 5% horse serum. Double dilutions of tested compounds were prepared using TECAN Genesis 150.[27] Bacteria were grown on appropriate agar plates (by Becton Dickinson. USA)—Columbia agar with 5% sheep blood for Streptococci and *M. catarrhalis*, Mueller–Hinton chocolate agar for *H. influenzae* and Mueller–Hinton agar for Staphylococci. Azithromycin was used as comparator.

4.3. NMR spectroscopy

The structure confirmations, complete ^1H and ^{13}C assignments, as well as the conformational analysis were made on basis of one- and two-dimensional NMR spectra (1H, APT, COSY, NOESY, ROESY, edited HSQC and HMBC). All NMR spectra were recorded on Bruker Avance III 600, Bruker Avance DRX500 and Bruker Avance DPX300 spectrometers, equipped with 5 mm diameter inverse and $^1H/^{13}C$ dual detection probes with z-gradient accessory. The spectra were acquired using standard Bruker pulse sequences in $CDCl_3$ and DMSO-d_6 at 25 °C with TMS as the internal standard. NOESY spectra were obtained with the mixing time of 400 ms.

4.4. Molecular modelling

Conformational analysis has been carried out using MOE2008.10 software package [MOE: The molecular operating environment from Chemical Computing Group Inc.]. MMFF94x force field was used with implicit distance dependent water solvation. Single point energies of first ten conformations were calculated at B3LYP/6-31G** level using Jaguar 7.6 program [Schroedinger, Inc.: Portland, OR, 1991–2000.]. Crystal structures for ABT-773[22] telithromycin[9,23] and azithromycin[9,15] as well as calculated conformations for compound **7a** were also superposed on their macrolactone rings using MOE software.

4.5. Chemistry

4.5.1. 6-(2-Amino-ethylamino)-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (3a) and 7-[(2-aminoethyl)amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (3b)

To the vigorously stirred solution of 1,2-diaminoethane (24 mL, 0.36 mol) in *N*,*N*-dimethylacetamide (600 mL) 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid **2** (50.0 g, 0.18 mol) was added in portions. Resulting heterogeneous mixture was stirred at 120 °C for 8 h, at rt for 2 h, and at 0 °C for 1 h. Formed precipitate was collected on filter, washed with water (2 × 200 mL), cold ethanol (2 × 200 mL) and dried at 110 °C. To the solution of crude product in 6% HCl (500 mL) was added charcoal and stirred at 85 °C for 1 h. Charcoal was filtered off, filtrate was cooled to 35–40 °C. Precipitate was collected on filter yielding hydrochloride salt of product **3a** (6.40 g, 22%). Mother liquors were cooled at 4 °C and stirred overnight. Second precipitate was collected on filter, washed with water (100 mL) and ethanol (100 mL) and dried at 110 °C yielding product **3b** (4.18, 15%).

Compound **3a**: MS(*m*/*z*): calcd MH^+ 322.76; found: 322.00.

HRMS calcd for $C_{15}H_{16}ClN_3O_3$ $(M+H)^+$ 322.0958; found 322.0919.

^{1}H NMR (500 MHz, DMSO): δ 8.61 (1H, 2‴-CH, s), 8.28 (1H, 8‴-CH, s), 7.45 (1H, 5‴-CH, s), 6.29 (1H, X_1-NH, t), 3.84 (1H, 11‴-CH, m), 3.54 (2H, L_6-CH_2, dq), 3.09 (2H, L_5-CH_2, t), 1.30 (2H, 15‴-CH_2, dq), 1.17 (2H, 16‴-CH_2, dq).

^{13}C NMR (75 MHz, DMSO): δ 176.76 (4‴-CO), 166.22 (12‴-CO), 146.21 (2‴-CH), 142.66 (6‴-C), 132.72 (9‴-C), 126.99 (10‴-C), 125.59 (7‴-C), 119.44 (8‴-CH), 106.47 (3‴-C), 103.03 (5‴-CH), 40.55 (L_6-CH_2), 37.40 (L_5-CH_2), 36.00 (11‴-CH), 7.54 (15‴, 16‴-CH).

IR (KBr) ν_{max}/cm^{-1}: 3381, 3088, 3010, 2976, 1723, 1606, 1549, 1496, 1450, 1356, 1336, 1268, 1233, 1191, 1090, 1063, 1032, 1010, 960, 887, 855, 804, 770, 691, 613.

Compound **3b**: MS(*m*/*z*): calcd 306.31; found: 306.03.

HRMS calcd for $C_{15}H_{16}FN_3O_3$ $(M+H)^+$ 306.1254; found 306.1213.

^{1}H NMR (500 MHz, DMSO): δ 8.57 (1H, 2‴-CH, s), 7.79 (1H, 5‴-CH, d), 7.16 (1H, 8‴-CH, d), 3.75 (1H, 11‴-CH, m), 3.33 (2H, L_6-CH_2, m), 2.84 (2H, L_5-CH_2, t), 1.31 (2H, 15‴-CH_2, dq), 1.14 (2H, 16‴-CH_2, m).

^{13}C NMR (125 MHz, DMSO): δ 176.22 (4‴-CO), 166.71 (12‴-CO), 151.24 (10‴-C), 149.21 (2‴-CH), 147.39 (7‴-C), 140.91 (9‴-C), 113.93 (6‴-C), 109.10 (5‴-CH), 109.02 (3‴-C), 96.86 (2‴-CH), 46.16 (L_6-CH_2), 40.22 (L_5-CH_2), 36.17 (11‴-CH), 7.50 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3399, 3317, 2964, 2963, 2130, 1622, 1561, 1524, 1477, 1393, 1367, 1311, 1294, 1239, 1172, 1114, 1038, 984, 951, 893, 825, 787, 732.

4.5.2. Methyl 6-[(2-aminoethyl) amino]-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-3-quinolinecarboxylate (4a)

A solution of 6-(2-amino-ethylamino)-7-chloro-1-cyclopropyl-4-oxo-1.4-dihydro-quinoline-3-carboxylic acid **3a** (1.5 g, 4.7 mmol) in 3% HCl in methanol (150 mL) was stirred at 70 °C for 24 h before being leached to pH 7 with 40% NaOH. Reaction mixture was filtered and solvent was removed under reduced pressure yielding the title compound **4a** (1.41 g, 90%) as a yellow solid.

MS(*m*/*z*): calcd MH^+ 335.79; found: 335.80.

HRMS calcd for $C_{16}H_{18}ClN_3O_3$ $(M+H)^+$ 336.1115; found 336.1112.

^{1}H NMR (500 MHz, DMSO): δ 8.40 (1H, 2‴-CH, s), 8.06 (1H, 8‴-CH, s), 7.80 (2H, L_4-NH, s), 7.38 (1H, 5‴-CH, s), 5.96 (1H, X_1-NH, t), 3.74 (3H, 13‴-H_3, s), 3.66 (1H, 11‴-CH, m), 3.47 (2H, L_6-CH, dq), 3.11 (2H, L_5-CH_2, t), 1.24 (2H, 15‴-CH_2, dq), 1.07 (2H, 16‴-CH_2, dq).

^{13}C NMR (125 MHz, DMSO): δ 172.50 (4‴-CO), 165.42 (12‴-CO), 147.19 (2‴-CH), 142.00 (6‴-C), 132.31 (9‴-C), 128.33 (10‴-C), 125.43 (7‴-C), 118.86 (8‴-CH), 108.42 (3‴-C), 105.09 (5‴-CH), 51.62 (13‴-CH_3), 41.05 (L_6-CH_2), 37.82 (L_5-CH_2), 35.13 (11‴-CH), 7.77 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3479, 3076, 3012, 2957, 1721, 1682, 1609, 1574, 1553, 1512, 1478, 1438, 1383, 1360, 1249, 1112, 1066, 1010.

4.5.3. Methyl 7-chloro-1-cyclopropyl-6-{[2-({[(1,1-dimethylethyl) oxy] carbonyl} amino) ethyl] amino}-4-oxo-1,4-dihydro-3-quinolinecarboxylate (5a)

To a stirred solution of 6-[(2-aminoethyl) amino]-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-3-quinolinecarboxylate **4a** (1.0 g, 3.0 mmol) in 1,4-dioxane (6 mL) was added H_2O (3 mL), 1 M NaOH (3 mL) and di-*tert*-butyl dicarbonate (715 mg, 3.3 mmol) at 0 °C, than allowed to gradually reach rt. Reaction mixture was stirred at room temperature for 1 h and than partitioned between EtAc (10 mL) and water (10 mL). Aqueous layer was acidified to pH 5.1 with 2 N HCl, than extracted with DCM (3 × 20 mL). The combine organic extracts were dried (K_2CO_3), filtered and solvent removed under reduced pressure. The residue was diluted with mixture of 10:1 hexane/EtAc and product was filtered, washed with 10:1 hexane/EtAc and dried to give title product **5a** (137 mg, 10.5%) as yellow solid product.

MS(*m*/*z*): calcd MH^+ 435.91; found: 435.99.

HRMS calcd for $C_{21}H_{26}ClN_3O_5$ $(M+H)^+$ 436.1639; found 436.1630.

^{1}H NMR (500 MHz, DMSO): δ 8.38 (1H, 2‴-CH, s), 8.04 (1H, 8‴-CH, s), 7.33 (1H, 5‴-CH, s), 7.10 (1H, L_4-NH, s), 5.84 (1H, L_7-NH, s), 3.73 (3H, 13‴-CH_3, s), 3.66 (1H, 11‴-CH, m), 3.25 (2H, L_6-CH_2, ov), 3.24 (2H, L_5-CH_2, ov), 1.39 (9H, L_1-CH_3, s), 1.24 (2H, 15‴-CH_2, dq), 1.07 (2H, 16‴-CH_2, dq).

^{13}C NMR (125 MHz, DMSO): δ 171.84 (4‴-CO), 164.91 (12‴-CO), 155.88 (L_3-CO), 146.35 (2‴-CH), 141.76 (6‴-C), 131.23 (9‴-C), 127.85 (10‴-C), 124.22 (7‴-C), 118.03 (8‴-CH), 107.67 (3‴-C), 103.95 (5‴-CH), 77.65 (L_2-CH_2), 50.94 (13‴-CH_3), 43.47 (L_6-CH_2), 38.27 (L_5-CH_2), 34.46 (11‴-CH), 27.96 (L_1-CH_3), 7.47 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3449, 2956, 1720, 1686, 1609, 1509, 1459, 1388, 1364, 1254, 1234, 1128, 1066, 1006.

4.5.4. 1,1-Dimethylethyl {2-[(7-chloro-1-cyclopropyl-3-{[(2-hydroxyethyl) amino] carbonyl}-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl}carbamate (6a)

To a stirred solution of 7-chloro-1-cyclopropyl-6-{[2-({[(1,1-dimethylethyl) oxy] carbonyl} amino) ethyl] amino}-4-oxo-1,4-dihydro-3-quinolinecarboxylate **5a** (137 mg, 0.3 mmol) in MeOH (1.3 mL) was added 2-amino-ethanol (1.3 mL) at 75 °C for 12 h. Solvent was removed under reduced pressure and residue was diluted by addition of DCM (10 mL) and water (10 mL). The aqueous phase was separated from the organic phase and extracted with DCM (2 × 10 mL). The combined organic layers were dried (K_2CO_3), filtered and solvent removed under reduced pressure to give title product **6a** (64 mg, 46%) as yellow solid.

MS(m/z): calcd MH^+ 464.95; found: 464.95.

HRMS calcd for $C_{22}H_{29}ClN_4O_5$ $(M+H)^+$ 465.1905; found 465.1905.

^1H NMR (300 MHz, DMSO): δ 10.10 (1H, L_4-NH, t), 8.55 (1H, 2‴-CH, s), 8.10 (1H, 8‴-CH, s), 7.38 (1H, 5‴-CH, s), 7.10 (1H, 17‴-NH, s), 5.91 (1H, L_7-NH, s), 4.81 (1H, 18‴-OH, s), 3.72 (1H, 11‴-CH, m), 3.51 (2H, 14‴-CH_2, s), 3.35 (2H, 13‴-CH_2, ov), 3.26 (2H, L_6-CH_2, ov), 3.26 (2H, L_5-CH_2, ov), 1.39 (9H, L_1-CH_3, s), 1.28 (2H, 15‴-CH_2, dq), 1.07 (2H, 16‴-CH_2, dq).

^{13}C NMR (75 MHz, DMSO): δ 174.26 (4‴-CO), 164.19 (12‴-CO), 156.10 (L_3-CO), 144.86 (2‴-CH), 141.88 (6‴-C), 131.71 (9‴-C), 127.13 (10‴-C), 124.93 (7‴-C), 118.20 (8‴-CH), 109.38 (3‴-C), 103.37 (5‴-CH), 77.81 (L_2-C), 59.94 (14‴-CH_2), 43.56 (L_6-CH_2), 41.12 (13‴-CH_2), 38.39 (L_5-CH_2), 34.77 (11‴-CH), 28.11 (L_1-CH_3), 7.28 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3397, 2975, 2932, 1704, 1652, 1598, 1549, 1507, 1363, 1253, 1169, 1074, 1038.

4.5.5. 6-[(2-Aminoethyl) amino]-7-chloro-1-cyclopropyl-*N*-(2-hydroxyethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxamide (7a)

To a stirred solution of 27-chloro-1-cyclopropyl-3-(2-hydroxyethylcarbamoyl)-4-oxo-1,4-dihydro-quinolin-6-ylamino-ethyl}-carbamic acid *tert*-butyl ester **6a** (132 mg, 0.3 mmol) in DCM (1.32 mL) was added CF_3COOH (1.32 mL). Reaction mixture was stirred at room temperature for 1 h before being quenched with H_2O (10 mL) and leached to pH 7 with 40% NaOH, than extracted with DCM (3 × 10 mL). The combined organic layers were dried (K_2CO_3), filtered and solvent removed under reduced pressure to give title product **7a** (127 mg, 99%) as brown solid.

MS(m/z): calcd MH^+ 364.83; found: 364.83.

HRMS calcd for $C_{17}H_{21}ClN_4O_3$ $(M+H)^+$ 365.1380; found 365.1378.

^1H NMR (500 MHz, DMSO): δ 10.10 (1H, L_4-NH, t), 8.56 (1H, 2‴-CH, s), 8.12 (1H, 8‴-CH, s), 7.44 (1H, 5‴-CH, s), 5.91 (1H, X_1-NH, s), 3.73 (1H, 11‴-CH, m), 3.51 (2H, 14‴-CH_2, t), 3.39 (2H, 13‴-CH_2, dq), 3.31 (2H, L_6-CH_2, ov), 2.94 (2H, L_5-CH_2, t), 1.27 (2H, 15‴-CH_2, dq), 1.06 (2H, 16‴-CH_2, m).

^{13}C NMR (75 MHz, DMSO): δ 174.98 (4‴-CO), 164.84 (12‴-CO), 145.66 (2‴-CH), 142.55 (6‴-C), 132.58 (9‴-C), 127.79 (10‴-C), 125.97 (7‴-C), 119.96 (8‴-CH), 110.14 (3‴-C), 104.53 (5‴-CH), 60.61 (14‴-CH_2), 43.99 (L_6-CH_2), 41.80 (13‴-CH_2), 39.25 (L_5-CH_2), 35.48 (11‴-CH), 7.28 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3363, 3078, 2928, 2872, 1651, 1598, 1549, 1505, 1482, 1455, 1354, 1262, 1240, 1192, 1138, 1070, 1038.

4.5.6. 4″-*O*-[3-({2-[(1-Cyclopropyl-1,4-dihydro-3-{[(2-hydroxyethyl)amino]carbonyl}-7-chloro-4-oxo-6-quinolyl)amino]-ethyl}amino)propanoyl]-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (8a)

To the stirred solution of **1** (506 mg, 0.6 mmol) in acetonitrile (7 mL) was added 6-[(2-aminoethyl)amino]-7-chloro-1-cyclopropyl-*N*-(2-hydroxyethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxamide **7a** (460 mg, 1.3 mmol), H_2O (0.574 mL) and Et_3N (0.229 mL). Reaction mixture was stirred at 80 °C for 24 h and diluted with EtAc (25 mL) and poured into satd $NaHCO_3$ (25 mL). The organic phase was separated from aqueous phase and the aqueous phase extracted with EtAc (2 × 25 mL). The combined organic extracts were washed (brine), dried (K_2CO_3), filtered and the solvent removed under reduced pressure. The residue diluted with mixture of 10:1 di-isopropyl-ether/EtAc and product was filtered, washed with 10:1 di-isopropyl-ether/EtAc and dried to give title product **8a** (472 mg, 67%) as beige solid product.

MS(m/z): calcd MH^+ 1167.88; found 1168.70.

HRMS calcd for $C_{58}H_{95}ClN_6O_{16}$ $(M+H)^+$ 1167.6571; found 1167.6658.

^1H NMR (500 MHz, $CDCl_3$): δ 10.41 (1H, 17‴-NH, t), 8.75 (1H, 2‴-CH, s), 7.96 (1H, 8‴-CH, s), 7.53 (1H, 5‴-CH, s), 5.17 (1H, 1″-H, d), 5.12 (1H, L_7-NH, t), 4.71 (1H, 4″-H, d), 4.70 (1H, 13-H, ov), 4.57 (1H, 1′-H, d), 4.41 (1H, 5″-H, m), 4.27 (1H, 3-H, t), 3.83 (2H, 14‴-CH_2, t), 3.68 (1H, 11-H, ov), 3.66 (1H, 5′-H, ov), 3.65 (1H, 5-H, ov), 3.62 (2H, 13‴-CH_2, ov), 3.49 (1H, 11‴-CH, m), 3.37 (2H, L_6-CH_2, dq), 3.31 (3H, 3″O–CH_3, s), 3.28 (1H, 2′-H, ov), 3.03 (2H, L_5-CH_2), 3.01 (2H, L_7-CH_2, t), 2.96 (2H, L_3-CH_2, t), 2.77 (1H, 2-H, dq), 2.71 (1H, 10-H, dq), 2.64 (1H, 3′-H, ov), 2.62 (1H, L_{2a}-CH, ov), 2.55 (1H, L_{2b}-CH, ov), 2.41 (1H, 9a-H, ov), 2.41 (1H, 2″a-H, ov), 2.38 (6H, 3́N-$(CH_3)_2$, s), 2.33 (3H, 9N–CH_3, s), 2.10 (1H, 8-H, ov), 2.05 (1H, 9b-H, ov), 2.00 (1H, 4-H, m), 1.89 (1H, 14a-H, m), 1.74 (1H, 7a-H, d), 1.63 (1H, 2″b-H, dd), 1.47 (1H, 14b-H, m), 1.34 (2H, 15‴-CH_2, d), 1.29 (3H, 6-CH_3, s), 1.27 (1H, 7b-H, ov), 1.21 (3H, 2-CH_3, ov), 1.19 (3H, 3″-CH_3, ov), 1.17 (2H, 16‴-CH_2, ov), 1.17 (3H, 5″-CH_3, d), 1.12 (3H, 5′-CH_3, ov), 1.09 (3H, 10-CH_3, ov), 1.07 (3H, 12-CH_3, ov), 1.04 (3H, 4-CH_3, d), 0.91 (3H, 8-CH_3, ov), 0.88 (3H, 15-CH_3, ov).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.64 (1-CO), 175.64 (4‴-CO), 172.28 (L_1-CO), 166.99 (12‴-CO), 145.46 (2‴-CH), 142.37 (6‴-C), 132.37 (9‴-C), 127.62 (10‴-C), 126.53 (7‴-C), 117.55 (8‴-CH), 110.16 (3‴-C), 104.98 (5‴-CH), 102.16 (1′-CH), 94.90 (1″-CH), 83.37 (5-CH), 78.93 (4″-CH), 78.08 (3-CH), 77.49 (13-CH), 74.35 (12-C), 74.04 (11-CH), 73.58 (6-C), 72.99 (3″-C), 71.02 (2′-CH), 70.06 (9-CH_2), 68.67 (5′-CH), 65.55 (3′-CH), 63.31 (14‴-CH_2), 62.99 (5″-CH), 62.44 (10-CH), 49.48 (3″O–CH_3), 47.64 (L_5-CH_2), 45.08 (2-CH), 44.52 (L_3-CH_2), 42.97 (13‴-CH_2), 42.90 (L_6-CH_2), 42.29 (7-CH_2), 41.70 (4-CH), 40.49 (3′N–$(CH_3)_2$), 36.45 (9N–CH_3), 35.08 (2″-CH_2), 34.78 (11‴-CH), 34.70 (L_2-CH_2), 28.94 (4′-CH_2), 27.41 (6-CH_3), 26.75 (8-CH), 22.00 (8-CH_3), 21.76 (3″-CH_3), 21.36 (5′-CH_3), 21.27 (14-CH_2), 17.94 (5″-CH_3), 16.23 (12-CH_3), 14.91 (2-CH_3), 11.26 (15-CH_3), 9.31 (4-CH_3), 8.05 (15‴, 16‴-CH_2), 7.59 (10-CH_3).

IR (KBr) ν_{max}/cm^{-1}: 3424, 2972, 2936, 2877, 1735, 1652, 1598, 1550, 1503, 1461, 1378, 1355, 1256, 1171, 1109, 1074, 1047, 1016.

4.5.7. 4″-*O*-[3-({2-[(1-Cyclopropyl-1,4-dihydro-3-{[(2-hydroxyethyl)amino]carbonyl}-7-chloro-4-oxo-6-quinolyl)amino]-ethyl}-methyl-amino)propanoyl]-9-deoxo-9a-methyl-9a-aza-9a-homoerytromycin A (9a)

To a stirred solution of **8a** (300 mg, 0.3 mmol) in chloroform (8.18 mL) was added 36% of HCHO (0.0393 mL, 1.0 mmol) and HCOOH (0.0359 mL, 5.1 mmol). Reaction mixture was stirred at the room temperature for 12 h and than at 30 °C for 8 h before being quenched with H_2O (10 mL) and leached to pH 9 with 40% NaOH, than extracted with DCM (3 × 15 mL). The combined organic layers were dried (K_2CO_3), filtered and solvent removed under reduced pressure. The residue diluted with mixture of 10:1 di-isopropyl-ether/EtOAc and product was filtered, washed with 10:1 di-isopropyl-ether/EtOAc and dried to give title product **9a** (215 mg, 71%) as yellow solid product.

MS(m/z): calcd MH^+1181.91; found: 1180.65.

HRMS calcd for $C_{59}H_{97}ClN_6O_{16}$ $(M+H)^+$ 1181.6728; found 1181.6753.

^1H NMR (500 MHz, $CDCl_3$): δ 10.57 (1H, 17‴-NH, t), 8.78 (1H, 2‴-CH, s), 7.85 (1H, 8‴-CH, d), 7.48 (1H, 5‴-CH, d), 7.13 (1H, 7‴-CH, dd), 5.22 (1H, 1″-CH, dd), 4.76 (1H, 4″-CH, d), 4.71 (1H, 13-H, dd), 4.58 (1H, 1′-H, d), 4.43 (1H, 5″-H, m), 4.27 (1H, 3-H, t), 3.83 (2H, 14‴-CH_2, t), 3.68 (1H, 11-H, ov), 3.63 (1H, 5′-H, ov), 3.62 (2H, 13‴-CH_2, ov), 3.61 (1H, 5-H, ov), 3.53 (1H, 11‴-CH, m), 3.32 (3H, 3″O–CH_3, s), 3.29 (1H, 2′-H, ov), 3.25 (2H, L_6-CH_2, ov), 2.76 (2H, L_3-CH_2, ov), 2.74 (1H, 2-H, ov), 2.71 (2H, L_5-CH_2, ov), 2.68 (1H, 10-H, ov), 2.56 (2H, L_2-CH_2, ov), 2.54 (1H, 9a-H, ov), 2.42 (1H, 2″a-H, ov), 2.40 (6H, 3′N–$(CH_3)_2$, s), 2.32 (3H, 9N–CH_3), 2.26 (3H, L_4-CH_3, s), 2.07 (1H, 9b-H, ov), 2.06 (1H, 8-H, ov), 2.00 (1H, 4-H, ov), 1.91 (1H, 14a-H, m), 1.74 (1H, 7a-H, d), 1.67 (1H, 2″b-H,

dd), 1.47 (1H, 14b-H, m), 1.31 (2H, 15‴-CH_2, ov), 1.29 (3H, 6-CH_3, s), 1.27 (1H, 7b-H, ov), 1.25 (1H, 4′a-H, ov), 1.23 (2H, 16‴-CH_2, ov), 1.21 (3H, 5′-CH_3, ov), 1.20 (3H, 2-CH_3, ov), 1.19 (3H, 5″-CH_3, ov), 1.16 (1H, 4′b-H, ov), 1.13 (3H, 3″-CH_3, s), 1.10 (3H, 10-CH_3, d) 1.09 (3H, 12-CH_3, s), 1.06 (3H, 4-CH_3, d), 0.91 (3H, 8-CH_3, ov), 0.89 (3H, 15-CH_3, ov).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.88 (1-CO), 176.18 (4‴-CO), 172.34 (L_1-CO), 167.55 (12‴-CO), 146.64 (6‴-C), 144.78 (2‴-CH), 132.97 (9‴-C), 129.00 (10‴-C), 121.40 (7‴-CH), 117.90 (8‴-CH), 109.83 (3‴-C), 104.75 (5‴-CH), 102.23 (1′-CH), 94.72 (1″-CH), 83.38 (5-CH), 78.93 (4″-CH), 77.77 (3-CH), 77.54 (13-CH), 74.27 (12-C), 73.63 (6-C), 73.62 (11-CH), 73.09 (3″-C), 70.98 (2′-CH), 70.05 (9-CH_2), 67.74 (5′-CH), 65.92 (3′-CH), 63.59 (14‴-CH_2), 63.04 (5″-CH), 62.60 (10-CH), 55.73 (L_5-CH_2), 52.63 (L_3-CH_2), 49.48 (3″O–CH_3), 45.22 (2-CH), 43.02 (13‴-CH_2), 42.25 (7-CH_2), 42.18 (4-CH), 41.50 (L_4-CH_3), 40.93 (L_6-CH_2), 40.38 (3′N–$(CH_3)_2$), 36.29 (9N–CH_3), 35.00 (2″-CH_2), 34.85 (11‴-CH), 32.93 (L_2-CH_2), 28.94 (4′-CH_2), 27.55 (6-CH_3), 26.79 (8-CH), 22.00 (8-CH_3), 21.80 (3″-CH_3), 21.36 (14-CH_2), 21.30 (5′-CH_3), 17.90 (5″-CH_3), 16.26 (12-CH_3), 14.57 (2-CH_3), 11.30 (15-CH_3), 9.19 (4-CH_3), 8.05 (15‴, 16‴-CH_2), 7.41 (10-CH_3).

IR (KBr) ν_{max}/cm^{-1}: 3409, 2972, 2936, 1736, 1655, 1598, 1551, 1502, 1477, 1459, 1378, 1356, 1257, 1170, 1108, 1075, 1047, 1016.

4.5.8. 4″-*O*-[3-({2-[(1-Cyclopropyl-1,4-dihydro-3-{[(2-hydroxyethyl)amino]carbonyl}-4-oxo-6-quinolyl)amino]ethyl}amino)-propanoyl]-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (10a)

To a stirred solution of **8a** (72 mg, 0.06 mmol) in MeOH (20 mL) was added 10% Pd/C catalyst (35 mg, 0.03 mmol) at room temperature under hydrogen atmosphere (5 Barr pressure) for 20 h. The catalyst was removed by filtration, and solvent under reduced pressure. Residue was diluted in H_2O (10 mL) and leached to pH 9 with 40% NaOH, than extracted with DCM (3 × 15 mL). The combined organic layers were dried (K_2CO_3), filtered and solvent removed under reduced pressure yielding title product **10a** (26 mg, 37%) as beige solid.

MS(m/z): calcd MH^+1133.43; found: 1132.0.

HRMS calcd for $C_{58}H_{96}N_6O_{16}$ $(M+H)^+$ 1133.6961; found 1133.7010.

^{1}H NMR (600 MHz, $CDCl_3$): δ 10.52 (1H, 17‴-NH, t), 8.76 (1H, 2‴-CH, d), 7.92 (1H, 8‴-CH, dd), 7.50 (1H, 5‴-CH, d), 7.12 (1H, 7‴-CH, dd), 5.19 (1H, 1″-H, dd), 4.74 (1H, 4″-H, ov), 4.70 (1H, 13-H, ov), 4.58 (1H, 1′-H, d), 4.43 (1H, 5″-H, m), 4.26 (1H, 3-H, t), 3.83 (2H, 14‴-CH_2, ov), 3.66 (1H, 5′-H, ov), 3.69 (1H, 11-H, ov), 3.64 (2H, 13‴-CH_2, ov), 3.63 (1H, 5-H, ov), 3.50 (1H, 11‴-CH, m), 3.34 (2H, L_6-CH_2, ov), 3.31 (3H, 3″O–CH_3, s), 3.30 (1H, 2′-H, ov), 2.99 (2H, L_5-CH_2, ov), 2.97 (2H, L_3-CH_2, ov), 2.77 (1H, 2-H, ov), 2.70 (1H, 3′-H, ov), 2.71 (1H, 10-H, ov), 2.64 (2H, L_2-CH_2, ov), 2.55 (1H, 9a-H, d), 2.43 (6H, 3′N–$(CH_3)_2$, s), 2.40 (1H, 2″a-H, ov), 2.33 (3H, 9N–CH_3, s), 2.08 (1H, 9b-H, t), 2.01 (1H, 8-H, ov), 2.00 (1H, 4-H, ov), 1.91 (1H, 14a-H, m), 1.74 (1H, 7a-H, ov), 1.73 (1H, 4′a-H, ov), 1.65 (1H, 2″b-H, dd), 1.47 (1H, 14b-H, m), 1.32 (2H, 15‴-CH_2, ov), 1.29 (3H, 6-CH_3, s), 1.28 (1H, 7b-H, ov), 1.24 (3H, 3″-CH_3, s), 1.19 (3H, 2-CH_3, ov), 1.19 (3H, 5″-CH_3, ov), 1.18 (2H, 16‴-CH_2, ov), 1.17 (1H, 4′b-H, ov), 1.12 (3H, 5′-CH_3, d), 1.10 (3H, 12-CH_3, s), 1.09 (3H, 10-CH_3, d), 1.04 (3H, 4-CH_3, d), 0.91 (3H, 8-CH_3, ov), 0.89 (3H, 15-CH_3, ov).

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.19 (4‴-CO), 171.61 (L_1-CO), 171.60 (1-CO) 167.46 (12‴-CO), 144.88 (2‴-CH), 144.12 (6‴-C), 132.32 (9‴-C), 128.82 (10‴-C), 121.32 (7‴-CH), 118.07 (8‴-CH), 109.71 (3‴-C), 105.37 (5‴-CH), 102.12 (1′-CH), 94.87 (1″-CH), 83.25 (5-CH), 78.93 (4″-CH), 77.96 (3-CH), 77.49 (13-CH), 74.33 (12-C), 73.84 (11-CH), 73.59 (6-C), 73.03 (3″-C), 71.00 (2′-CH), 70.04 (9-CH_2), 67.67 (5′-CH), 65.55 (3′-CH), 63.67 (14‴-CH_2), 62.97 (5″-CH), 62.50 (10-CH), 49.48 (3″O–CH_3), 47.73 (L_5-CH_2), 45.07 (2-CH), 44.43 (L_3-CH_2), 43.02 (13‴-CH_2), 42.61 (L_6-CH_2), 42.23 (7-CH_2), 41.71 (4-CH), 40.43 (3′N–$(CH_3)_2$), 36.45 (9N–CH_3), 35.07 (2″-CH), 34.80 (11‴-CH), 34.11 (L_2-CH_2), 28.94 (4′-CH_2), 27.37 (6-CH_3), 26.74 (8-CH), 21.99 (8-CH_3), 21.72 (3″-CH_3), 21.38 (14-CH_2), 21.21 (5′-CH_3), 17.92 (5″-CH_3), 16.21 (12-CH_3), 14.84 (2-CH_3), 11.27 (15-CH_3), 9.33 (4-CH_3), 8.03 (15‴, 16‴-CH_2), 7.57 (10-CH_3).

IR (KBr) ν_{max}/cm^{-1}: 3418, 3080, 2972, 2937, 2877, 1732, 1651, 1622, 1599, 1556, 1496, 1456, 1380, 1346, 1255, 1172, 1109, 1974, 1046, 1016.

4.5.9. 4″-*O*-[3-({2-[(1-Cyclopropyl-1,4-dihydro-3-{[(2-hydroxyethyl)amino]carbonyl}-4-oxo-6-quinolyl)amino]ethyl}-methylamino)propanoyl]-9-deoxo-9a-methyl-9a-aza-9a-homoerytromycin A (10b)

To a stirred solution of **9a** (100 mg, 0.085 mmol) in MeOH (20 mL) was added 10% Pd/C catalyst (50 mg, 0.05 mmol) at room temperature under hydrogen atmosphere (5 bar pressure) for 24 h. The catalyst was removed by filtration, and solvent under reduced pressure. Residue was diluted in H_2O (10 mL) and leached to pH 9 with 40% NaOH, than extracted with DCM (3 × 10 mL). The combined organic layers were dried (K_2CO_3), filtered and solvent removed under reduced pressure yielding title product **10b** (52 mg, 54%) as white solid.

MS(m/z): calcd MH^+1147.46; found: 1147.84.

HRMS calcd for $C_{59}H_{98}N_6O_{16}$ $(M+H)^+$ 1147.7118; found 1147.7190.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.57 (1H, 17‴-NH, t), 8.78 (1H, 2‴-CH, s), 7.85 (1H, 8‴-CH, d), 7.48 (1H, 5‴-CH, d), 7.13 (1H, 7‴-CH, dd), 5.22 (1H, 1″-CH, dd), 4.76 (1H, 4″-CH, d), 4.71 (1H, 13-H, dd), 4.58 (1H, 1′-H, d), 4.43 (1H, 5″-H, m), 4.27 (1H, 3-H, t), 3.83 (2H, 14‴-CH_2, t), 3.68 (1H, 11-H, ov), 3.63 (1H, 5′-H, ov), 3.62 (2H, 13‴-CH_2, ov), 3.61 (1H, 5-H, ov), 3.53 (1H, 11‴-CH, m), 3.32 (3H, 3″O–CH_3, s), 3.29 (1H, 2′-H, ov), 3.25 (2H, L_6-CH_2, ov), 2.76 (2H, L_3-CH_2, ov), 2.74 (1H, 2-H, ov), 2.71 (2H, L_5-CH_2, ov), 2.68 (1H, 10-H, ov), 2.56 (2H, L_2-CH_2, ov), 2.54 (1H, 9a-H, ov), 2.42 (1H, 2″a-H, ov), 2.40 (6H, 3́N-$(CH_3)_2$, s), 2.32 (3H, 9N–CH_3), 2.26 (3H, L_4-CH_3, s), 2.07 (1H, 9b-H, ov), 2.06 (1H, 8-H, ov), 2.00 (1H, 4-H, ov), 1.91 (1H, 14a-H, m), 1.74 (1H, 7a-H, d), 1.67 (1H, 2″b-H, dd), 1.47 (1H, 14b-H, m), 1.31 (2H, 15‴-CH_2, ov), 1.29 (3H, 6-CH_3, s), 1.27 (1H, 7b-H, ov), 1.25 (1H, 4′a-H, ov), 1.23 (2H, 16‴-CH_2, ov), 1.21 (3H, 5′-CH_3, ov), 1.20 (3H, 2-CH_3, ov), 1.19 (3H, 5″-CH_3, ov), 1.16 (1H, 4′b-H, ov), 1.13 (3H, 3″-CH_3, s), 1.10 (3H, 10-CH_3, d) 1.09 (3H, 12-CH_3, s), 1.06 (3H, 4-CH_3, d), 0.91 (3H, 8-CH_3, ov), 0.89 (3H, 15-CH_3, ov).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.88 (1-CO), 176.18 (4‴-CO), 172.34 (L_1-CO), 167.55 (12‴-CO), 146.64 (6‴-C), 144.78 (2‴-CH), 132.97 (9‴-C), 129.00 (10‴-C), 121.40 (7‴-CH), 117.90 (8‴-CH), 109.83 (3‴-C), 104.75 (5‴-CH), 102.23 (1′-CH), 94.72 (1″-CH), 83.38 (5-CH), 78.93 (4″-CH), 77.77 (3-CH), 77.54 (13-CH), 74.27 (12-C), 73.63 (6-C), 73.62 (11-CH), 73.09 (3″-C), 70.98 (2′-CH), 70.05 (9-CH_2), 67.74 (5′-CH), 65.92 (3′-CH), 63.59 (14‴-CH_2), 63.04 (5″-CH), 62.60 (10-CH), 55.73 (L_5-CH_2), 52.63 (L_3-CH_2), 49.48 (3″O–CH_3), 45.22 (2-CH), 43.02 (13‴-CH_2), 42.25 (7-CH_2), 42.18 (4-CH), 41.50 (L_4-CH_3), 40.93 (L_6-CH_2), 40.38 (3′N–$(CH_3)_2$), 36.29 (9N–CH_3), 35.00 (2″-CH_2), 34.85 (11‴-CH), 32.93 (L_2-CH_2), 28.94 (4′-CH_2), 27.55 (6-CH_3), 26.79 (8-CH), 22.00 (8-CH_3), 21.80 (3″-CH_3), 21.36 (14-CH_2), 21.30 (5′-CH_3), 17.90 (5″-CH_3), 16.26 (12-CH_3), 14.57 (2-CH_3), 11.30 (15-CH_3), 9.19 (4-CH_3), 8.05 (15‴, 16‴-CH_2), 7.41 (10-CH_3).

IR (KBr) ν_{max}/cm^{-1}: 3418, 2972, 2937, 2877, 1732, 1651, 1622, 1600, 1556, 1497, 1456, 1380, 1346, 1321, 1255, 1172, 1109, 1074, 1045, 1016.

4.5.10. Methyl 7-[(2-aminoethyl) amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylate (4b)

A solution of 7-[(2-aminoethyl)amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid **3b** (2.0 g, 6.5 mmol) in H_2SO_4 (16 mL) in methanol (132 mL) was stirred at 75 °C for 48 h before being evaporated to 1/3 of its volume and leached to pH 7 with 40% NaOH. Reaction mixture was filtered and precipitate washed with MeOH yielding the title compound **4b** (1.5 g, 72%) as white solid.

MS(m/z): calcd MH^+319.34; found: 319.90.

HRMS calcd for $C_{16}H_{18}FN_3O_3$ $(M+H)^+$ 320.1410; found 320.1424.

^{1}H NMR (600 MHz, DMSO): δ 8.39 (1H, 2‴-CH, s), 7.69 (1H, 5‴-CH, d), 7.03 (1H, 8‴-CH, d), 6.68 (1H, L_7-NH, t), 3.73 (3H, X-$_{13}$, CH_3, s), 3.60 (1H, 11‴-CH, m), 3.51 (2H, L_6-CH_2, m), 3.11 (2H, L_5-CH_2, t), 1.27 (2H, 15‴-CH_2, dq), 1.07 (2H, 16‴-CH_2, m).

^{13}C NMR (75 MHz, DMSO): δ 171.40 (4‴-CO), 165.03 (12‴-CO), 147.77 (10‴-C), 147.51 (2‴-CH), 140.35 (7‴-C), 139.00 (9‴-C), 117.43 (6‴-C), 109.56 (5‴-CH), 108.73 (3‴-C), 96.73 (8‴-CH), 51.10 (13‴-CH_3), 39.44 (L_6-CH_2), 37.16 (L_5-CH_2), 34.69 (11‴-CH), 7.50 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3563, 3455, 3417, 3093, 3006, 2962, 1720, 1635, 1596, 1553, 1525, 1494, 1441, 1395, 1370, 1351, 1321, 1303, 1259, 1237, 1207, 1186, 1162, 1139, 1099, 1059, 1004.

4.5.11. Methyl 1-cyclopropyl-7-{[2-({[(1,1-dimethylethyl) oxy] carbonyl} amino) ethyl]amino}-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylate (5b)

To a stirred solution of 7-[(2-aminoethyl) amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylate **4b** (1.5 g, 4.7 mmol) in 1,4-dioxane (18 mL) was added H_2O (4.5 mL), 1 M NaOH (4.5 mL) and di-*tert*-butyl dicarbonate (488 mg, 2.2 mmol) at 0 °C, than allowed to gradually reach rt. Reaction mixture was stirred at room temperature for 48 h. To the cooled reaction mixture was added new amount of di-*tert*-butyl dicarbonate (244 mg, 1.1 mmol), than allowed to gradually reach rt and stirred at room temperature for 12 h before filtered and solvent removed under reduced pressure. The residue diluted with mixture of 10:1 diisopropyl ether/EtOAc and product was filtered, washed with 10:1 diisopropyl ether/EtOAc and dried to give title product **5b** (640 mg, 32%) as white solid product.

MS(m/z): calcd MH^+ 420.12; found: 419.45.

HRMS calcd for $C_{21}H_{26}FN_3O_5$ $(M+H)^+$ 420.1935; found 420.1934.

^{1}H NMR (300 MHz, DMSO): δ 8.37 (1H, 2‴-CH, s), 7.65 (1H, 5‴-H, d), 7.16 (1H, 8‴-CH, d), 7.10 (1H, L_4-NH, t), 6.84 (1H, L_7-*NH*, s), 3.72 (3H, 13‴-CH_3, s), 3.60 (1H, 11‴-H, m), 3.28 (2H, L_6-CH2, ov), 3.20 (2H, L_5-CH_2, t), 1.37 (9H, L_1-CH_3, s), 1.29 (2H, 15‴-CH_2, d), 1.06 (2H, 16‴-CH_2, m).

^{13}C NMR (75 MHz, DMSO): δ 171.46 (4‴-CO), 165.10 (12‴-CO), 155.88 (L_3-CO), 147.64 (10‴-C), 147.40 (2‴-CH), 140.80 (7‴-C), 139.15 (9‴-C), 117.00 (6‴-C), 109.34 (5‴-CH), 108.53 (3‴-CH), 96.42 (8‴-CH), 77.81 (L_2-CH), 51.07 (13‴-CH_3), 42.34 (L_6-CH_2), 38.16 (L_5-CH_2), 34.77 (11‴-CH), 28.10 (L_1-CH_3), 7.47 (11‴, 12‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3374, 2976, 1729, 1696, 1635, 1619, 1575, 1525, 1491, 1458, 1434, 1394, 1364, 1347, 1313, 1269, 1235, 1159, 1113, 1083, 1003.

4.5.12. 1,1-Dimethylethyl {2-[(1-cyclopropyl-6-fluoro-3-{[(2-hydroxyethyl) amino] carbonyl}-4-oxo-1,4-dihydro-7-quinolinyl)amino]ethyl}carbamate (6b)

To a stirred solution of 1-cyclopropyl-7-{[2-({[(1,1-dimethylethyl) oxy] carbonyl} amino) ethyl]amino}-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylate **5b** (600 mg, 14.3 mmol) in MeOH (5.5 mL) was added 2-amino-ethanol (5.5 mL) at 75 °C for 12 h. To the stirred reaction mixture was added new amount of 2-amino-ethanol (5.5 mL) and stirred for 12 h. Solvent was removed under reduced pressure and residue was diluted by addition of DCM (25 mL) and water (25 mL). The aqueous phase was separated from the organic phase and extracted with DCM (2 × 25 mL). The combined organic layers were dried (K_2CO_3), filtered and solvent removed under reduced pressure to give title product **6b** (350 mg, 55%) as brown solid.

MS(m/z): calcd MH^+448.50; found: 449.12.

HRMS calcd for $C_{22}H_{29}FN_4O_5$ $(M+H)^+$ 449.220; found 449.2192.

^{1}H NMR (500 MHz, DMSO): δ 10.10 (1H, L_4-NH, t), 8.54 (1H, 2‴-CH, s), 7.73 (1H, 5‴-CH, d), 7.20 (1H, 8‴-CH, d), 7.07 (1H, 17‴-NH, t), 6.77 (1H, L_7-NH, t), 3.66 (1H, 11‴-CH, m), 3.50 (2H, 14‴-CH_2, t), 3.38 (2H, 13‴-CH_2, ov), 3.31 (2H, L_6-CH_2, ov), 3.20 (2H, L_5-CH_2, dq), 1.37 (9H, L_1-CH_3, s), 1.32 (2H, 15‴-CH_2, d), 1.05 (2H, 16‴-CH_2, m).

^{13}C NMR (75 MHz, DMSO): δ 176.32 (4‴-CO), 166.53 (12‴-CO), 158.19 (L_3-CO), 150.05 (10‴-C), 147.92 (2‴-CH), 143.43 (7‴-CH), 141.86 (9‴-C), 118.19 (6‴-C), 111.96 (3‴-C), 111.30 (5‴-CH), 98.39 (8‴-CH), 80.12 (L_2-CH), 62.28 (14‴-CH_2), 44.66 (L_6-CH_2), 43.42 (13‴-H_2), 40.42 (L_5-CH_2), 37.23 (11‴-CH), 30.39 (L_1-CH_3), 9.77 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3350, 2974, 2941, 2883, 1702, 1660, 1635, 1601, 1552, 1524, 1491, 1391, 1365, 1338, 1317, 1303, 1274, 1257, 1171, 1124, 1070, 1036.

4.5.13. 7-[(2-Aminoethyl) amino]-1-cyclopropyl-6-fluoro-*N*-(2-hydroxyethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxamide (7b)

To a stirred solution of 1,1-dimethylethyl {2-[(1-cyclopropyl-6-fluoro-3-{[(2-hydroxyethyl) amino] carbonyl}-4-oxo-1,4-dihydro-7-quinolinyl)amino]ethyl}carbamate **6b** (300 mg, 0.7 mmol) in DCM (20 mL) was added CF_3COOH (3 mL). Reaction mixture was stirred at room temperature for 1 h before being leached to pH 7 with 40% NaOH, and formed precipitate filtered and dried at 60 °C for 1 h to give title product **7b** (436 mg, 99%) as white solid.

MS(m/z): calcd MH^+ 349.09; found: 348.38.

HRMS calcd for $C_{17}H_{21}FN_4O_3$ $(M+H)^+$ 349.1676; found 349.1657.

^{1}H NMR (500 MHz, DMSO): δ 10.10 (1H, L_4-NH, t), 8.54 (1H, 2‴-CH, s), 7.77 (1H, 5‴-CH, d), 7.10 (1H, 8‴-CH, d), 6.84 (1H, L_7-NH, t), 3.68 (1H, 11‴-CH, m), 3.58 (2H, L_6-CH_2, dq), 3.50 (2H, 14‴-CH_2, t), 3.37 (2H, 13‴-CH_2, ov), 3.11 (2H, L_5-CH_2, t), 1.31 (2H, 15‴-CH_2, d), 1.06 (2H, 16‴-CH_2, m).

^{13}C NMR (125 MHz, DMSO): δ 173.61 (4‴-CO), 163.75 (12‴-CO), 148.10 (10‴-C), 145.32 (2‴-CH), 140.40 (7‴-C), 139.00 (9‴-C), 115.97 (6‴-C), 109.32 (3‴-C), 108.80 (5‴-CH), 95.94 (8‴-CH), 59.52 (14‴-CH_2), 40.68 (13‴-CH_2), 39.60 (L_6-CH_2), 36.83 (L_5-CH_2), 34.47 (11‴-CH), 7.05 (15‴, 16‴-CH_2).

IR (KBr) ν_{max}/cm^{-1}: 3423, 3347, 1686, 1652, 1630, 1600, 1561, 1526, 1493, 1466, 1432, 1392, 1355, 1331, 1311, 1210, 1183, 1128, 1061, 1043.

4.5.14. 4″-*O*-[3-({2-[(1-Cyclopropyl-1,4-dihydro-6-fluoro-3-{[(2-hydroxyethyl)amino]carbonyl}-4-oxo-7-quinolyl)amino]ethyl}-amino)propanoyl]-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin (9a)

To the stirred solution of **1** (277 mg, 0.3 mmol) in acetonitrile (4 mL) was added 7-(2-amino-ethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (2-hydroxy-ethyl)-amide **7b** (240 mg, 0.7 mmol), H_2O (0.3 mL) and Et_3N (0.1 mL). Reaction mixture was stirred at 80 °C for 12 h and diluted with EtAc (25 mL) and poured into sat. $NaHCO_3$ (25 mL). The organic phase was separated from aqueous phase and the aqueous phase extracted with EtAc (2 × 25 mL). The combined organic extracts were washed (brine), dried (K_2CO_3), filtered and the solvent removed under reduced pressure. The residue diluted with mixture of 10:1 di-isopropyl-ether/EtAc and product was filtered, washed with 10:1 di-isopropyl-ether/EtAc and dried to give title product **8b** (121 mg, 30%) as beige solid product.

MS(m/z): calcd MH^+ 1151.42; found: 1151.42.

HRMS calcd for $C_{58}H_{95}FN_6O_{16}$ $(M+H)^+$ 1151.6867; found 1151.6864.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.46 (1H, 17‴-NH, t), 8.33 (1H, 2‴-CH, s), 7.89 (1H, 5‴-CH, d), 6.94 (1H, 8‴-CH,), 5.26 (1H, L_7-NH, dq), 5.21 (1H, 1″-H, d), 4.72 (1H, 4″-H, ov), 4.71 (1H, 13-H, ov), 4.55 (1H, 1′-H, d), 4.44 (1H, 5″-H, m), 4.27 (1H, 3-H, t), 3.82 (2H, 14‴-CH_2, t), 3.78 (1H, 5′-H, m), 3.68 (1H, 11-H, d), 3.60 (1H, 5-H, ov), 3.59 (2H, 13‴-CH_2, ov), 3.43 (1H, 11‴-CH, m), 3.34 (2H, L_6-CH_2, ov), 3.32 (3H, 3″O–CH_3, s), 3.24 (1H, 2′-H, dd), 3.03 (2H, L_5-CH_2, t), 2.97 (2H, L_3-CH_2, t), 2.75 (1H, 2-H, dq), 2.69 (1H, 10-H, dq), 2.60 (1H, L_{2a}-CH, t), 2.55 (1H, L_{2b}-CH, ov), 2.54 (1H, 3′-H, ov), 2.53 (1H, 9a-H, ov), 2.41 (1H, 2″a-H, d), 2.31 (3H, 9N–CH_3, s), 2.30 (6H, 3́N-$(CH_3)_2$, s), 2.06 (1H, 8-H, ov), 2.04 (1H, 9b-H, ov), 2.00 (1H, 4-H, ov), 1.90 (1H, 14a-H, m), 1.76 (1H, 7a-H, d), 1.69 (1H, 4′a-H, ov), 1.63 (1H, 2″b-H, ov), 1.46 (1H, 14b-H, m), 1.31 (2H, 15‴-CH_2, ov), 1.29 (3H, 6-CH_3, s), 1.28 (1H, 7b-H, ov), 1.23 (1H, 4′b-H, ov), 1.21 (3H, 5′-CH_3, d), 1.19 (3H, 2-CH_3, d), 1.19 (2H, 16‴-CH_2, ov), 1.18 (3H, 5″-CH_3, d), 1.11 (3H, 3″-CH_3, ov), 1.10 (3H, 12-CH_3, ov), 1.09 (3H, 10-CH_3, ov), 1.05 (3H, 4-CH_3, d), 0.91 (3H, 8-CH_3, ov), 0.89 (3H, 15-CH_3, ov).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.97 (1-CO), 175.35 (4‴-CO), 172.44 (L_1-CO), 167.11 (12‴-C), 148.41 (10‴-C), 146.22 (2‴-CH), 141.57 (7‴-C), 139.61 (9‴-C), 117.50 (6‴-C), 110.47 (3‴-C), 110.18 (5‴-CH), 102.39 (1′-CH), 95.88 (8‴-CH), 94.59 (1″-CH), 83.08 (5-CH), 79.09 (4″-CH), 77.71 (3-CH), 77.70 (13-CH), 74.24 (12-C), 73.66 (6-C), 73.54 (11-CH), 72.95 (3″-C), 70.97 (2′-CH), 70.11 (9-CH_2), 67.85 (5′-CH), 65.58 (3′-CH), 63.38 (14‴-CH_2), 62.94 (5″-CH), 62.58 (10-CH), 49.53 (3″O–CH_3), 47.66 (L_5-CH_2), 45.23 (2-CH), 44.58 (L_3-CH_2), 43.00 (13‴-CH_2), 42.21 (4-CH), 42.21 (7-CH_2), 42.21 (L_6-CH_2), 40.38 (3′N–$(CH_3)_2$), 36.23 (9N–CH_3), 34.94 (2″-CH_2), 34.84 (11‴-CH), 34.62 (L_2-CH_2), 29.10 (4′-CH_2), 27.59 (6-CH_3), 26.80 (8-CH), 21.32 (3″-CH_3), 21.99 (8-CH_3), 21.85 (5′-CH_3), 21.32 (14-CH_2), 17.85 (3″-CH_3), 16.23 (5″-CH_3), 14.50 (12-CH_3), 14.28 (2-CH_3), 11.28 (15-CH_3), 9.04 (4-CH_3), 8.21 (15‴, 16‴-CH_2), 7.32 (10-CH_3).

IR (KBr) ν_{max}/cm^{-1}: 3418, 3093, 2972, 2937, 2877, 2833, 1732, 1652, 1633, 1606, 1556, 1521, 1489, 1463, 1380, 1337, 1309, 1292, 1257, 1172, 1111, 1074, 1045, 1016.

4.5.15. 4″-*O*-[3-({2-[(1-Cyclopropyl-1,4-dihydro-3-{[(2-hydroxyethyl)amino]carbonyl}-4-oxo-7-quinolyl)amino]ethyl}amino)-propanoyl]-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin (9b)

To a stirred solution of **8b** (100 mg, 0.09 mmol) in chloroform (3,6 mL) were added 36% of HCHO (0.0133 mL, 0.48 mmol) and HCOOH (0.0121 mL, 0.32 mmol). Reaction mixture was stirred at 30 °C for 2 h and then at the room temperature for 48 h before being quenched with H_2O (10 mL) and leached to pH 9 with 40% NaOH, than extracted with DCM (3 × 10 mL), The combined organic layers were dried (K_2CO_3), filtered and solvent removed under reduced pressure. The residue diluted with mixture of 10:1 di-isopropyl-ether/EtAc and product was filtered, washed with 10:1 di-isopropyl-ether/EtAc and dried to give title product **9b** (60 mg, 59%) as beige solid product.

MS(m/z): calcd MH^+ 1165.45; found: 1163.79.

HRMS calcd, for $C_{59}H_{97}FN_6O_{16}$ $(M+H)^+$ 1165.7023; found 1165.7119.

^{1}H NMR (600 MHz, $CDCl_3$): δ 10.51 (1H, 17‴-NH, t), 8.75 (1H, 2‴-CH, s), 7.95 (1H, 5‴-CH, dd), 6.93 (1H, 8‴-CH, dd), 5.36 (1H, L_7-NH, dq), 5.20 (1H, 1″-H, d), 4.72 (1H, 4″-H, ov), 4.70 (1H, 13-H, ov), 4.58 (1H, 1′-H, d), 4.41 (1H, 5″-H, m), 4.26 (1H, 3-H, t), 3.82 (2H, 14‴-CH_2, t), 3.68 (1H, 11-H, ov), 3.67 (1H, 5′-H, ov), 3.61 (1H, 5-H, ov), 3.60 (2H, 13‴-CH_2, ov), 3.44 (1H, 11‴-CH, m), 3.32 (2H, L_6-CH_2, ov), 3.32 (3H, 3″O–CH_3, s), 3.30 (1H, 2′-H, ov), 2.80 (2H, L_3-CH_2, ov), 2.78 (1H, 2-H, ov), 2.76 (2H, L_5-CH_2, ov), 2.70 (1H, 10-H, ov), 2.59 (2H, L_2-CH_2, ov), 2.54 (1H, 9a-H, d), 2.51 (6H, 3′N$(CH_3)_2$), 2.40 (1H, 2″a-H, d), 2.33 (3H, 9N–CH_3, s), 2.30 (3H, L_4-CH_3, s), 2.08 (1H, 9b-H, ov), 2.04 (1H, 8-H, ov), 2.00 (1H, 4-H, ov), 1.90 (1H, 14a-H, m), 1.75 (1H, 7a-H, d), 1.65 (1H, 2″b-H, dd), 1.44 (1H, 14b-H, m), 1.32 (2H, 15‴-CH_2, ov), 1.30 (1H, 7b-H, ov), 1.29 (3H, 6-CH_3, s), 1.25 (1H, 4′b-H, ov), 1.21 (3H, 5′-CH_3, d), 1.20 (3H, 2-CH_3, d), 1.20 (2H, 16‴-CH_2, ov), 1.17 (3H, 5″-CH_3, d), 1.12 (3H, 3″-CH_3, d), 1.11 (3H, 10-CH_3, d), 1.09 (3H, 12-CH_3, s), 1.04 (3H, 4-CH_3, s), 0.91 (3H, 8-CH_3, ov), 0.90 (3H, 15-CH_3, ov).

^{13}C NMR (150 MHz, $CDCl_3$): δ 179.00 (1-CO), 175.40 (4‴-CO), 171.99 (L_1-CO), 167.34 (12‴-CO), 149.27 (10‴-C), 146.17 (2‴-CH), 141.50 (7‴-C), 139.69 (9‴-C), 117.50 (6‴-C), 110.46 (3‴-C), 110.28 (5‴-CH), 102.50 (1′-CH), 95.84 (8‴-CH), 94.82 (1″-CH), 83.39 (5-CH), 78.98 (4″-CH), 77.97 (3-CH), 77.22 (13-CH), 74.31 (12-C), 73.56 (11-CH), 73.22 (6-C), 73.16 (3″-C), 71.03 (2′-CH), 70.00 (9-CH_2), 63.74 (14‴-CH_2), 62.97 (10-CH), 62.97 (5″-CH), 55.31 (L_5-CH_2), 52.64 (L_3-CH_2), 49.47 (3″O–CH_3), 45.09 (2-CH), 43.12 (13‴-CH_2), 42.28 (4-CH), 42.28 (7-CH_2), 41.49 (L_4-CH_3), 40.50 (3′N–CH_3), 40.05 (L_6-CH_2), 36.42 (9N–CH_3), 35.04 (2″-CH_2), 34.84 (11‴-CH), 32.75 (L_2-CH_2), 29.69 (4′-CH_2), 27.33 (6-CH_3), 26.74 (8-CH), 21.99 (8-CH_3), 21.68 (5′-CH_3), 21.18 (14-CH_2), 21.18 (3″-CH_3), 17.85 (5″-CH_3), 16.21 (12-CH_3), 14.50 (2-CH_3), 11.27 (15-CH_3), 9.05 (4-CH_3), 8.14 (15‴, 16‴-CH_2), 7.11 (10-CH_3).

IR (KBr) ν_{max}/cm^{-1}: 3418, 3091, 2972, 2937, 2875, 1732, 1659, 1652, 1633, 1605, 1553, 1520, 1488, 1379, 1337, 1308, 1257, 1172, 1110, 1076, 1045, 1016.

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