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Synthesis of macrolones with central piperazine ring in the linker and its influence on antibacterial activity

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ABSTRACT

Three macrolides, clarithromycin, azithromycin and 11-*O*-Me-azithromycin have been selected for the construction of a series of new macrolone derivatives. Quinolone-linker intermediates are prepared by Sonogashira-type C(6)-alkynylation of 6-iodoquinolone precursors. The final macrolones, differing by macrolide moiety and substituents at the position *N*-1 of the quinolone or by the presence of an ethyl ester or free acid on the quinolone unit attached via a linker.

The linker comprises of a central piperazine ring bonded to the 4″-*O* position of cladinose by 3-carbon ester or ether functionality. Modifications of the linker did not improve antibacterial properties compared to the previously reported macrolone compounds. Linker flexibility seems to play an important role for potency against macrolide resistant respiratory pathogens.

1. Introduction

As the utility of currently used antibiotics becomes compromised by the emergence and subsequent spread of resistant pathogens, there is a continuous need for the development of novel antibacterial agents with broader spectrum of activity, able to combat resistance.

The well-known antibiotic erythromycin A has been used in the clinic for the treatment of upper respiratory tract infections since the 1950s.[1] Since then, erythromycin and the second generation macrolides, such as clarithromycin and azithromycin, have been extensively used for the treatment of upper and lower respiratory tract infections caused by Gram-positive bacteria.[2]

In 1995 a novel series of macrolides known as ketolides was introduced.[3,4] These compounds possess a 3-keto and 11,12-carbamate functionalities with tethered aromatic groups to the macrolide cores. Location of the aryl group on the ketolide scaffold is considered to be a very important feature for their antibacterial activity. Ketolides showed excellent potency against the majority of the key macrolide resistant respiratory pathogens.[5,6]

In order to obtain derivatives with improved potency against resistant Gram-positive and relevant Gram-negative strains, we have recently reported a novel class of antibacterial compounds, named macrolones.[7–11]

This term describes compounds which consist of a macrolide scaffold with a quinolone unit covalently attached via suitable linker (Fig. 1). We have studied the SAR trends based on differences in macrolide moiety, length of the linker with combinations of heteroatoms nitrogen and oxygen, positions of binding of the linker to the quinolone-3-carboxylic unit and substitutions at *N*-1 position of the quinolone unit, as well as the influence of different quinolone moieties.

It has been shown that elongation of the chain improved potency against key respiratory pathogens resistant to currently used macrolide antibiotics, especially MLS_B resistant strains of *S. pyogenes*. Some representatives of this class of compounds are presented at Figure 1.

Here we report the synthesis and the structure–activity relationships of derivatives having piperazine in the aliphatic linker. These structures were characterized by the C–C bond at the position C-6 of the quinolone-3-carboxylic acid unit and a central piperazine ring in the linker. Incorporation of a piperazine ring restricts the conformational flexibility of the linker compared to the acyclic analogues. However, flexibility of distal parts towards macrolide and quinolone units remains unchanged. Additional stabilization of molecule was achieved by substituting the 4″-ester bond by an ether bond.[12] Ester derivatives have been prepared

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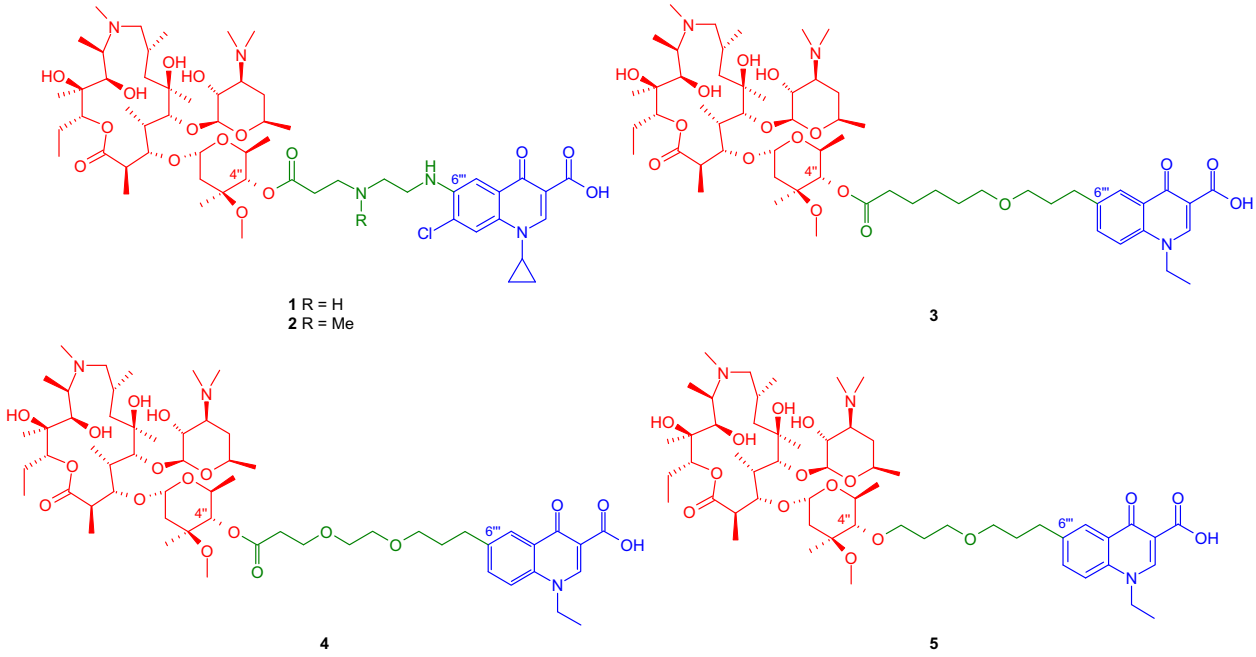


Figure 1. Structures of the recently reported macrolone derivatives.

on clarithromycin, azithromycin and 11-*O*-methyl-azithromycin. The influence of different substituents at *N*-1, as well as the impact of triple, double or single bonds in the linker or the presence of a C-3 carboxylic group or ester on the quinolone on the antimicrobial potency are also reported. It was expected that these structures would provide guidance for future research. Macrolones reported in this paper are presented by the general formula in Figure 2.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthetic route to the target 4″-*O* ester macrolone derivatives

(i) *Quinolone intermediate synthesis.* Construction of the linker started from commercially available 1,1-dimethylethyl 1-piperazinecarboxylate **1** which was quantitatively propargylated to give intermediate **3**, that was subjected to Sonogashira type[13,14] of C–C coupling with 6-iodoquinolone-3-carboxylic acid derivatives **4–6**.[14–17]

This reaction afforded derivatives **8** and **9** in 80–90% yields that were isolated by a precipitation from *n*-hexane/EtOAc (ratio 10/1).

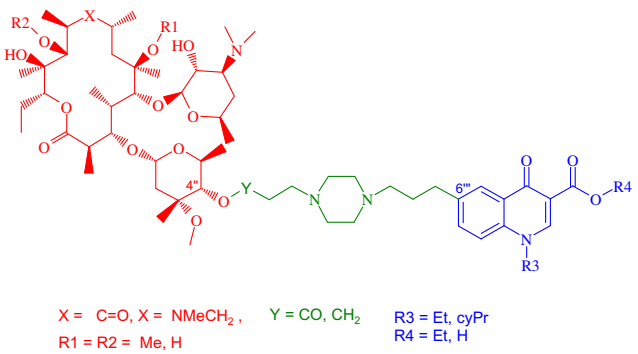


Figure 2. General formula of synthesized derivatives.

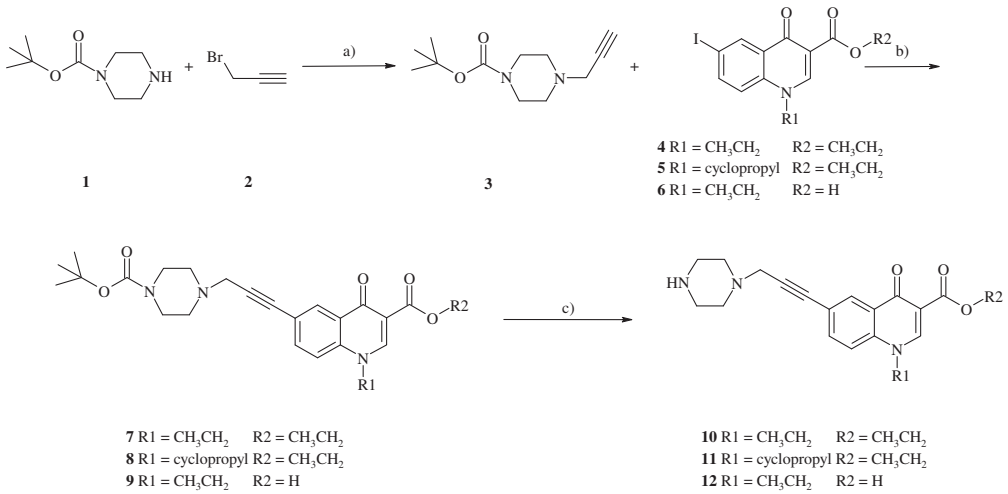
Derivative **7** was isolated by a column chromatography over silica gel in 22% yield. Deprotection of amine carbamates **7–9** with trifluoroacetic acid gave amine derivatives **10–12** in quantitative yields (Scheme 1).[18]

(ii) *Macrolide chemistry.* Clarithromycin and azithromycin, used for the preparation of starting molecules **13–15** in Scheme 2, are commercially available, whereas 11-*O*-methyl-azithromycin[19,20] was prepared as reported previously. For the synthesis of compounds **18–20**, **14** was used as its 2′-*O*-acetyl derivative. Preparation of the 4″-*O*-propenoyl esters **13–15** was achieved by reaction of starting macrolide and 3-chloropropenoyl chloride in the presence of triethylamine as base.[21] Subsequent Michael reaction and removal of the 2′-*O*-acetyl protecting group was used to prepare compounds **18–20**.[22] Alternatively the 2′-*O*-acetyl protection can be removed prior to Michael addition and this route afforded target compounds **16, 17** and **21**.[21]

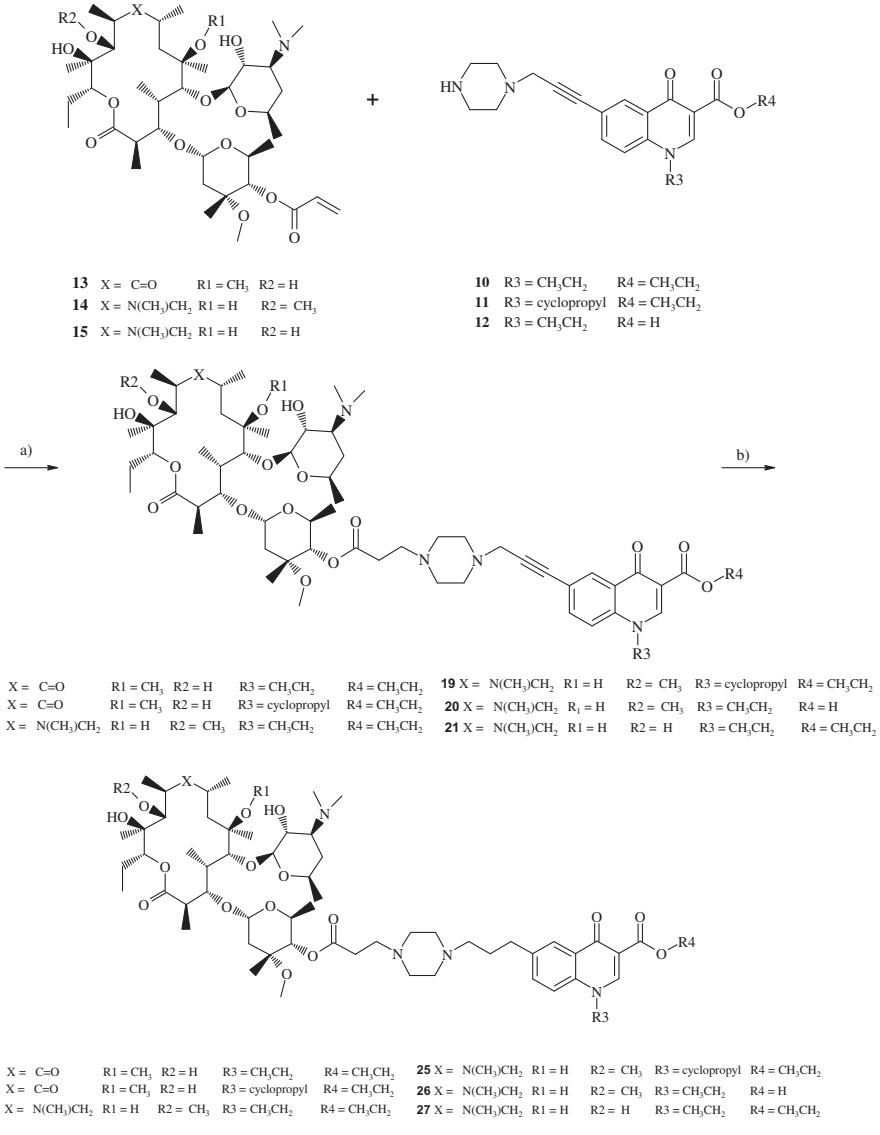
Michael addition proceeded in a mixture of MeCN/H_2O (ratio 10/1) with excess of quinolone-3-carboxylic acid derivatives **10–12** and TEA at 80 °C for 24 h. Products **16–21** were isolated by column chromatography on silica-gel in moderate yields. It was assumed that low yields for 11-*O*-methylazithromycin derivatives are due to sterical hindrance caused by conformational change. Triple bond in the aliphatic chain was catalytically hydrogenated over 10% Pd/C in MeOH at 5 bar of hydrogen. This procedure avoided any over-hydrogenation or hydrogenolysis affording analogues **22–27** in low to moderate yields.

2.1.2. Synthetic route to the target 4″-*O* ether macrolone derivatives

(i) *Quinolone intermediate synthesis.* Intermediate **29** was prepared starting from propargyl alcohol **28** and ethyl 1-ethyl-6-iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylate **4** by Sonogashira cross-coupling.[13,14] This reaction was completed with 92% yield and the product **29** was isolated by precipitation from *n*-hexane/EtOAc (ratio 10/1). Catalytic hydrogenation of alkyne **29** over a Lindlar catalyst gave the (*Z*)-alkene **30** in quantitative yield. Alcohol **30** was converted into the *tert*-butyl carbonate **32** which was used as electrophile[23,24] for the Pd-catalyzed N-alkylation of cyclic amine **33** to afford **34** in quantitative yield. A modified procedure



Scheme 1. Synthesis of quinolone intermediates **10–12.** Reagents and conditions: (a) MeCN, Na_2CO_3, 0–50 °C, 24 h; (b) CuI, Pd(II)PPh_3Cl_2, TEA, MeCN, 50 °C, N_2, 2 h; (c) CF_3COOH/CH_2Cl_2 = 1/1, rt, 1 h.



Scheme 2. Synthesis of macrolone intermediates **22–27.** Reagents and conditions: (a) TEA, H_2O/MeCN, 80 °C, 24 h; (b) 10% Pd/C, MeOH, 5 bar, rt, 20 h.

was presented in the synthesis of ketolide antibiotic ABT-773[25] for selective 6-O-alkylation which was originally demonstrated in carbohydrate chemistry.[26,27] Deprotection of *tert*-butyl carbamate **34** was completed by brief treatment with trifluoroacetic acid as described for compounds **10–12**[18] to afford compound **35** in quantitative yield (Scheme 3).

(ii) *Macrolide chemistry.* Protected 4″-*O*-ether azithromycin derivate **36** was prepared in five steps from commercially available azithromycin, as previously reported.[10] Dess–Martin oxidation[28,29] of γ-hydroxy group at **36** was performed in DCM at room temperature[22,23] for 3 h to afford intermediate **37**. The product was not isolated and reductive alkylation was performed in situ with 2 equiv of amine **35** and $NaBH(OAc)_3$–$ZnCl_2$ as reducing agent. Derivativee **38** was isolated by column chromatography over silica-gel in 28% yield. One-pot deprotection and ester hydrolysis under basic condition was carried out in $MeOH/H_2O$ (ratio 3/1) with 18 equiv of K_2CO_3 at 50 °C for 5 h to obtain compound **39**. In the final step, the alkene in the linker was catalytically hydrogenated with 10% Pd/C in MeOH at a pressure of 5 bar and rt affording compound **40** (Scheme 4).

2.1.3. NMR spectroscopy details

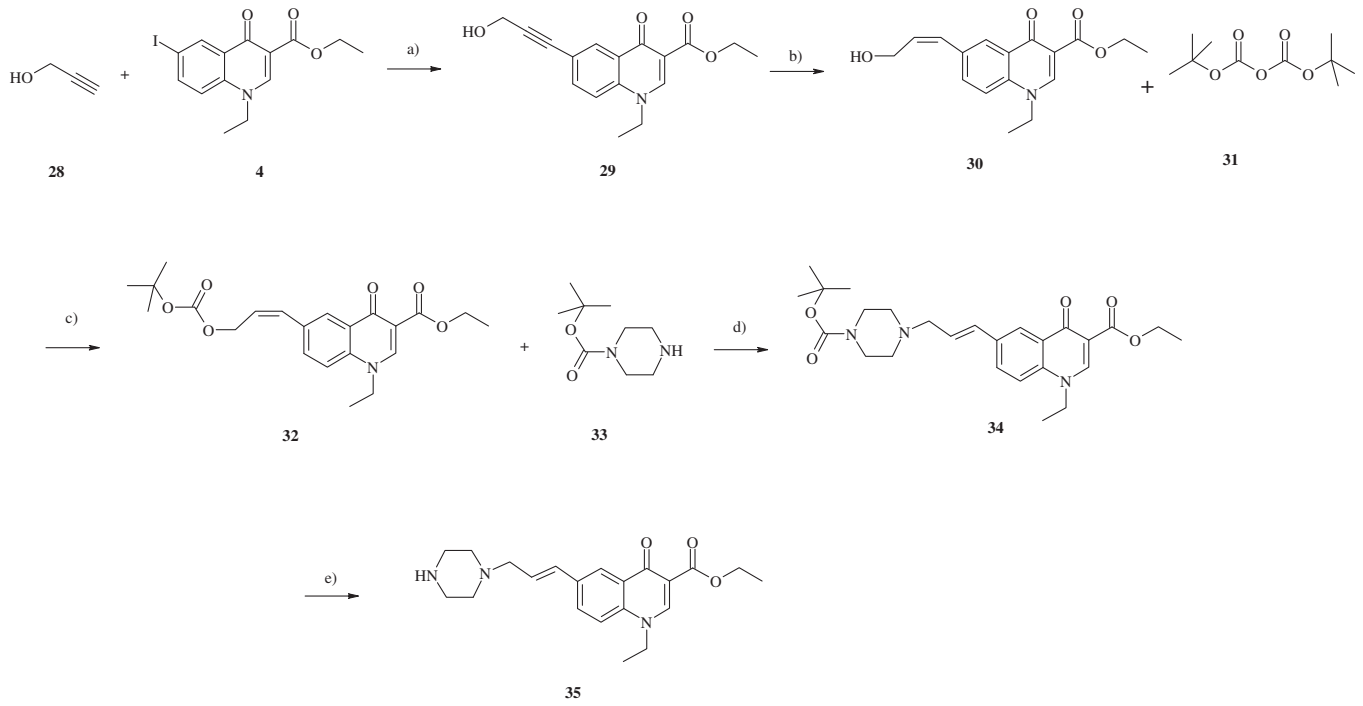
The structural assignments for the newly created structures were confirmed by NMR studies. Atom numbering of quinolone and macrolone derivatives is shown at Figure 3.

A downfield shift of 4″-H signal from 3.04 ppm in azithromycin and 3.00 in clarithromycin to 4.70 ppm in 4″-ester macrolones **16–27** and an upfield shift to 2.78 ppm for 4″-ether macrolones **38–40** was observed.[30,31] These observations are consistent with the 4″-O forming part an ester or ether function respectively. It was noted that the 4″-H proton in compounds **16–27** resonates as a doublet, not as a triplet as in the parent macrolides, in accordance with acylation of a free hydroxyl group at 4″ position, that is, lack of the 4″-H and 4″-OH coupling. The appearance of 4″-H signals for ether derivatives **38–40** at 2.78 ppm and disappearance of ^{13}C signal at 176 ppm for C=O were clear evidence of ether bond present on the cladinose moiety. In ^1H NMR spectra of **30** and **32**, the arising of L_{11}-CH and L_{12}-CH proton signals in the downfield ranges of 5.89–5.91 ppm and 6.54–6.80 ppm, respectively, indicated presence of double C–C bond in the aliphatic linker. The configuration of L_{11}–L_{12} double bond in the structures of compounds **30–32** is *Z*, indicated by the coupling constants $^3J_{L11\text{-}H,L12\text{-}H}$ 12 Hz. The configuration of the L_{11}–L_{12} double bond in the structures of compounds **34–39** is *E* as indicated by the coupling constants $^3J_{L11\text{-}H,L12\text{-}H}$ 16 Hz. This stereochemistry is consistent with mechanic aspects of allylic amination.[31–34]

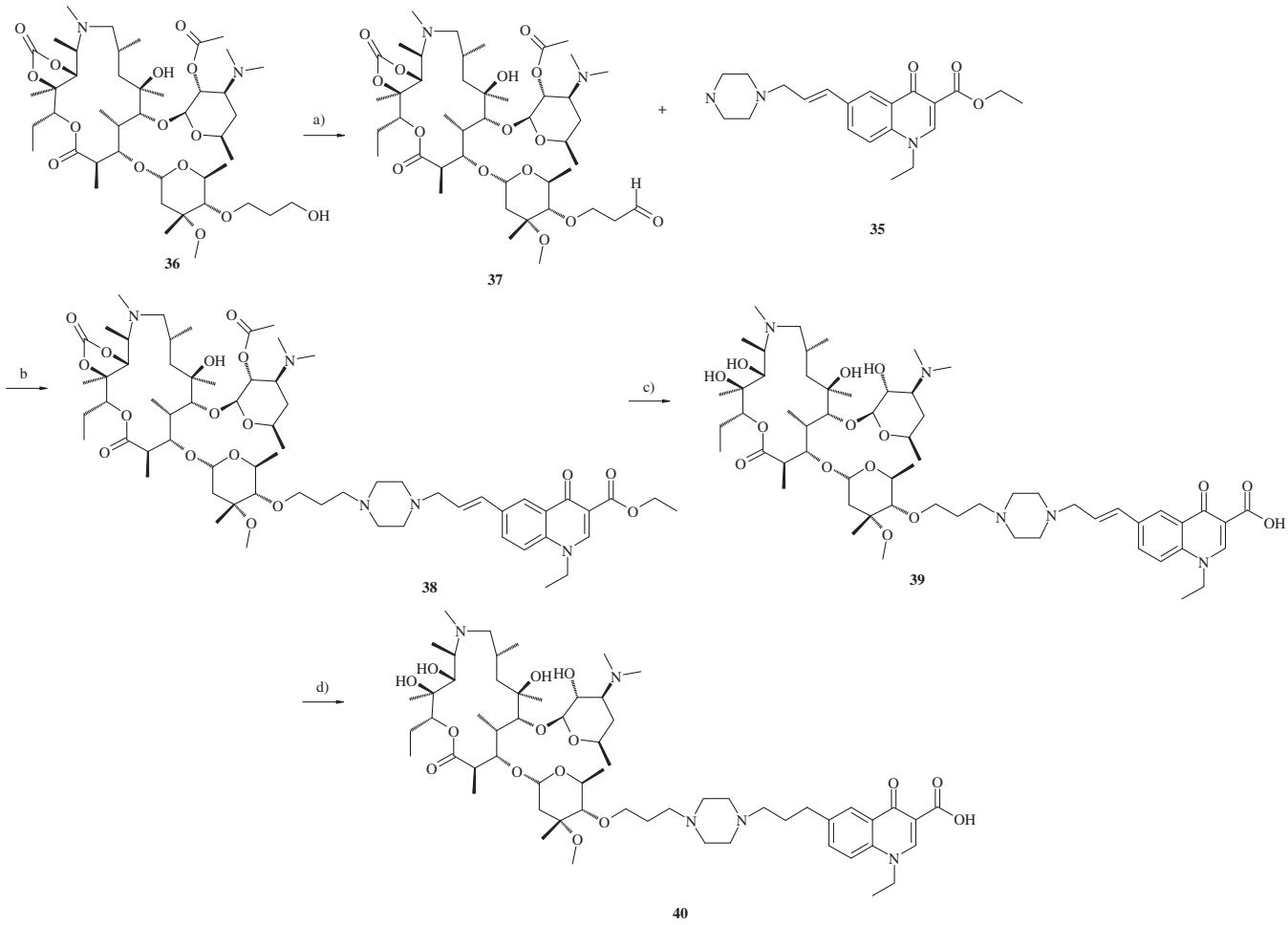
In addition, the NMR spectra showed the presence of the expected signals arising from the quinolone and piperazine atoms. In the ^1H NMR spectra of **7–9**, having *tert*-butylcarboxylate protecting group, two methylene groups of piperrazine resonate at 3.35 ppm, while the other two at 2.50 ppm, due to their chemical non equivalence. In the ^1H NMR spectra of **10–27**, the arising of piperazine proton signals in the narrow ranges 2.68–2.74 ppm and 2.45–2.55 ppm respectively, are clear evidence of the equivalence of protons. Similarly, piperazine protons in **34** were observed at the range of 2.77–3.33 ppm, in constant to that in **35** at 2.37–2.39 ppm and in macrolone derivatives **38–40** at 2.52–2.60 ppm.

2.2. Antibacterial activity

Antibacterial activity of compounds was determined by a standard broth microdilution method.[35] Azithromycin and clarithromycin were used as controls. The results are shown in Tables 1 and 2 and are expressed as minimum inhibitory concentrations (MICs) in units of μg/mL. The organisms tested represented 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. Macrolide resistance was due to two major mechanisms—production of efflux pumps (M), or ribosome modification by methylation. Methylase expression was inducible (iMLS) or constitutive (cMLS).



Scheme 3. Synthesis of quinolone intermediate **35.** Reagents and conditions: (a) Cu(I)I, $Pd(II)PPh_3Cl_2$, TEA, MeCN, 50 °C, N_2; (b) 5% $Pd/CaCO_3$-Pb, MeOH, 1 bar, rt, 4 h; (c) *n*-Bu_4NHSO_4, 1 M aq NaOH, DCM, 0–25 °C, 20 h; (d) $Pd_2(dba)_3$, dppb, dry toluene, reflux, 3 h; (e) TFA, DCM, rt, 2.5 h.



Scheme 4. Synthesis of macrolone intermediates **38**–**40.** Reagents and conditions: (a) Dess–Martin periodinane, DCM, rt, 3 h; (b) $NaBH(OAc)_3$, $ZnCl_2$, rt, 20 h; (c) MeOH/H_2O = 3/1, K_2CO_3, 50 °C, 5 h, rt, 20 h; (d) 10% Pd/C, MeOH, 5 bar, rt, 20 h.

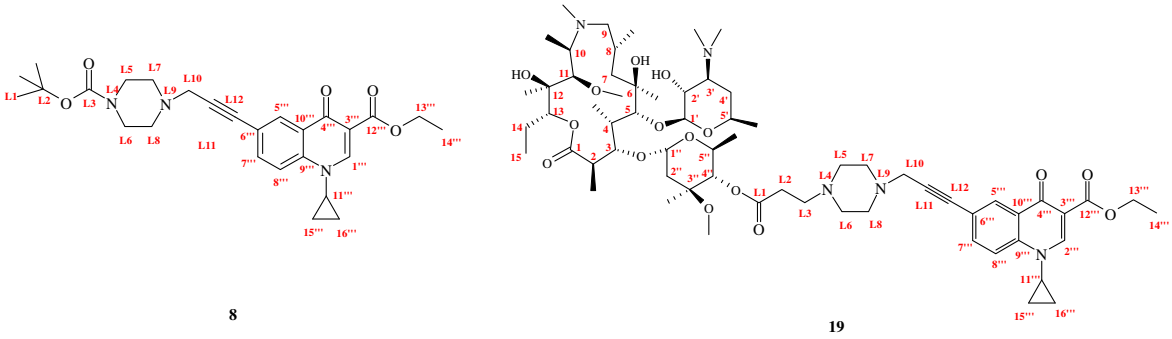


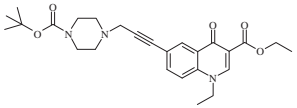
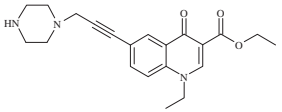
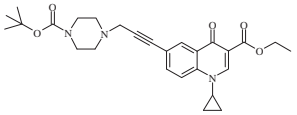
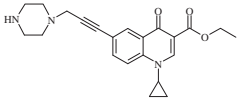
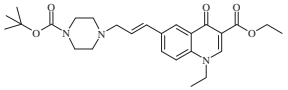
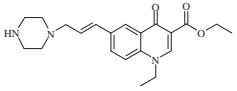
Figure 3. Chemical numbering of quinolone derivative **8** and macrolone derivative **19** as examples.

All quinolone intermediates were antibacterially inactive (Table 1).

Across the scaffolds, quinolone ester macrolones with triple bond in the linker had better antibacterial activity against Gram positive organisms than their reduced counterparts (**16** vs **22**, **17** vs **23**, **21** vs **27**, **18** vs **24**, **19** vs **25**), Table 2. Regarding Gram negatives, situation is less straightforward and potency of compounds is comparable (**17** vs **23** and **19** vs **25**), better for triple bonded (**16** vs **22**) or better for reduced equivalents (**21** vs **27** and **18** vs **24**, against *M. catarrhalis*). The presence of free carboxylic acid, rather than ester group on quinolone moiety (**20** vs **18** and **26** vs **24**) resulted in improved potency, which is most pronounced on efflux resistant *S. aureus* (from >64 μg/mL for **18** and **24**, to 0.5, and 0.25 for **20** and **26**, respectively) and *H. influenzae*. However, on the 11-*O*-methyl azithromycin scaffold potency of acid **20** against methylase expressing pneumococcal strains was diminished. Quinolone esters were mostly inactive against efflux resistant *S. aureus*, while displaying good potency against efflux resistant streptococcal species. Triple-bonded compounds were slightly more active than their corresponding reduced counterparts.

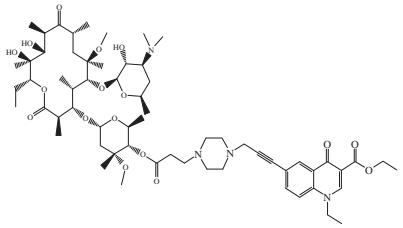
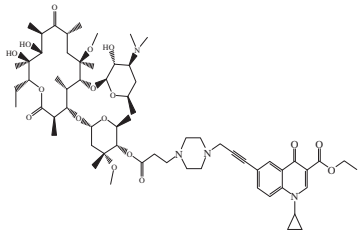
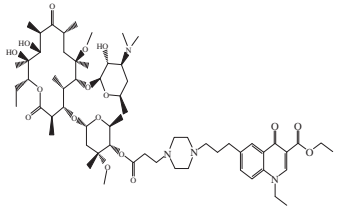
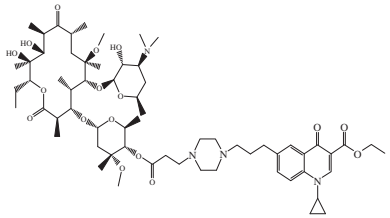
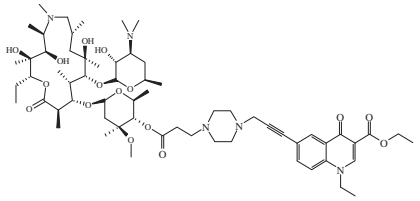
Replacement of ethyl by a cyclopropyl at the *N*-1 position of the quinolone did not improve antibacterial activity of either triple-bonded or reduced derivative in the clarithromycin or 11-*O*-methyl analogues.

Table 1
In vitro antibacterial activity of quinolone intermediates (MIC values in μg/mL)

	Phenotype	*S. aureus* ATCC 13709 ery S	*S. pneumoniae* SP030 ery S	*S. pyogenes* 3565 ery S	*S. aureus* 90256/97 iMLS	*S. pneumoniae* 134 GR-Micro iMcLS	*S. pyogenes* Finland 11 iMLS	*S. aureus* PK2 cMLS	*S. pneumoniae* 58 Spain cMLS	*S. pyogenes* 166 GR-Micro cMLS	*S. aureus* PK1 M	*S. pneumoniae* Ci137 M	*S. pyogenes* 3 Finland M	*H. influenzae* ATCC 49247	*M. catarrhalis* ATCC 23246
AZM		0.5	⩽0.125	⩽0.125	>64	>64	16	>64	>64	>64	>64	8	8	1	⩽0.125
CAM		0.25	⩽0.125	⩽0.125	>64	>64	1	>64	>64	>64	32	4	4	8	⩽0.125
7		>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
10		>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
8		>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
11		>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
34		>64	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
35		>64	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

AZM = azithromycin; CAM = clarithromycin; iMLS = inducible resistance to macrolide, licosamide and streptogramin (MLS) antibiotics; iMcL = inducible resistance to macrolide and constitutive resistance to lincosamide antibiotics; cMLS = constitutive MLS resistance; M = efflux mediated macrolide resistance.

Table 2
In vitro antibacterial activity of macrolones (MIC values in μg/ml)

	Phenotype	*S. aureus* ATCC 13709 ery S	*S. pneumoniae* SP030 ery S	*S. pyogenes* 3565 ery S	*S. aureus* 90256/97 iMLS	*S. pneumoniae* 134 GR-Micro iMcLS	*S. pyogenes* Finland 11 iMLS	*S. aureus* PK2 cMLS	*S. pneumoniae* 58 Spain cMLS	*S. pyogenes* 166 GR-Micro cMLS	*S. aureus* PK1 M	*S. pneumoniae* Ci137 M	*S. pyogenes* 3 Finland M	*H. influenzae* ATCC 49247	*M. catarrhalis* ATCC 23246
AZM		0.5	⩽0.125	⩽0.125	>64	>64	16	>64	>64	>64	>64	8	8	1	⩽0.125
CAM		0.25	⩽0.125	⩽0.125	>64	>64	1	>64	>64	>64	32	4	4	8	⩽0.125
16		0.25	⩽0.125	⩽0.125	>64	1	⩽0.125	>64	⩽0.125	8	32	⩽0.125	—	4	1
17		4	⩽0.125	⩽0.125	>64	4	0.5	>64	4	16	>64	⩽0.125	⩽0.125	>64	4
22		4	⩽0.125	⩽0.125	>64	16	0.25	>64	8	16	>64	⩽0.125	⩽0.125	>64	4
23		4	⩽0.125	⩽0.125	>64	16	0.5	>64	4	16	>64	⩽0.125	⩽0.125	>64	4
21		1	⩽0.125	⩽0.125	>64	⩽0.125	⩽0.125	>64	⩽0.125	32	16	⩽0.125	⩽0.125	4	1

(*continued on next page*)

Table 2 (*continued*)

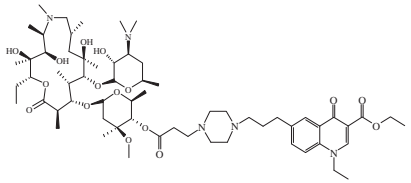
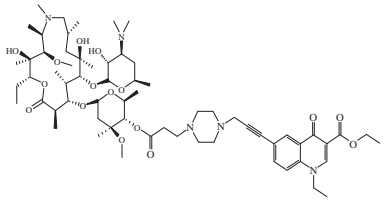
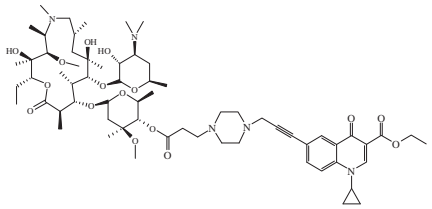
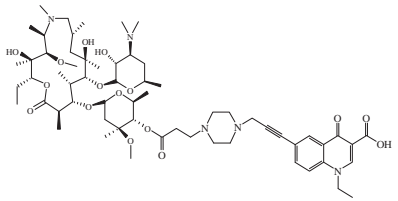
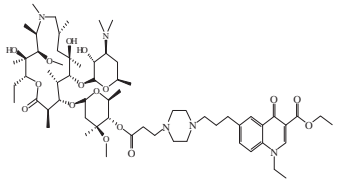
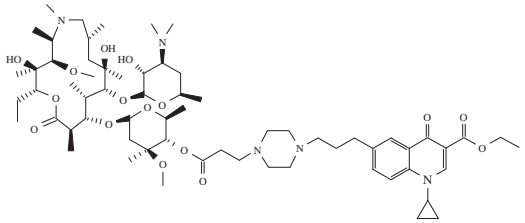
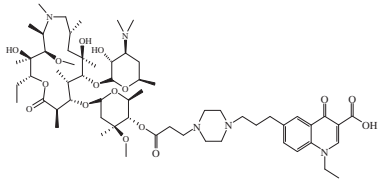
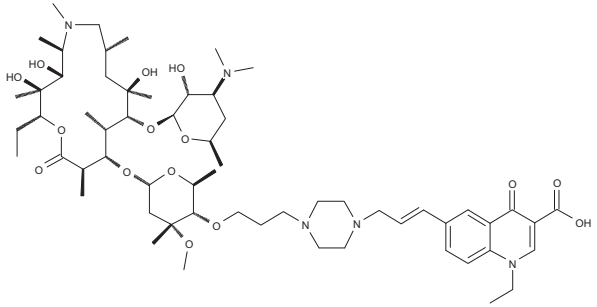
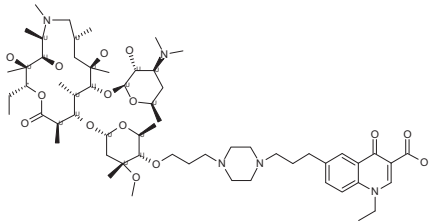
	Phenotype	*S. aureus* ATCC 13709 ery S	*S. pneumoniae* SP030 ery S	*S. pyogenes* 3565 ery S	*S. aureus* 90256/97 iMLS	*S. pneumoniae* 134 GR-Micro iMcLS	*S. pyogenes* Finland 11 iMLS	*S. aureus* PK2 cMLS	*S. pneumoniae* 58 Spain cMLS	*S. pyogenes* 166 GR-Micro cMLS	*S. aureus* PK1 M	*S. pneumoniae* Ci137 M	*S. pyogenes* 3 Finland M	*H. influenzae* ATCC 49247	*M. catarrhalis* ATCC 23246
27		1	⩽0.125	⩽0.125	>64	⩽0.125	⩽0.125	>64	⩽0.125	32	64	⩽0.125	0.5	2	0.25
18		4	⩽0.125	⩽0.125	>64	0.5	0.25	>64	1	32	>64	⩽0.125	1	32	8
19		4	⩽0.125	⩽0.125	>64	0.25	⩽0.125	>64	0.5	32	64	⩽0.125	0.5	16	4
20		0.25	⩽0.125	⩽0.125	8	8	⩽0.125	>64	4	16	0.5	⩽0.125	⩽0.125	1	0.5
24		4	⩽0.125	⩽0.125	>64	32	2	>64	8	>64	>64	2	2	32	0.25
25		4	⩽0.125	⩽0.125	>64	>64	0.25	>64	32	32	>64	⩽0.125	1	16	

Table 2 (*continued*)

	Phenotype	*S. aureus* ATCC 13709 ery S	*S. pneumoniae* SP030 ery S	*S. pyogenes* 3565 ery S	*S. aureus* 90256/97 iMLS	*S. pneumoniae* 134 GR-Micro iMcLS	*S. pyogenes* Finland 11 iMLS	*S. aureus* PK2 cMLS	*S. pneumoniae* 58 Spain cMLS	*S. pyogenes* 166 GR-Micro cMLS	*S. aureus* PK1 M	*S. pneumoniae* Ci137 M	*S. pyogenes* 3 Finland M	*H. influenzae* ATCC 49247	*M. catarrhalis* ATCC 23246
26		⩽0.125	⩽0.125	⩽0.125	4	16	⩽0.125	>64	⩽0.125	32	0.25	⩽0.125	⩽0.125	1	0.5
39		2	⩽0.125	⩽0.125	>64	>64	1	>64	32	64	8	8	4	16	0.5
40		8	⩽0.125	0.5	>64	32	4	>64	8	>64	32	0.25	8	32	

AZM = azithromycin; CAM = clarithromycin; iMLS = inducible resistance to macrolide, licosamide and streptogramin (MLS) antibiotics; iMcL = inducible resistance to macrolide and constitutive resistance to lincosamide antibiotics; cMLS = constitutive MLS resistance; M = efflux mediated macrolide resistance.

Two compounds with the quinolone carboxylic acid attached to azithromycin scaffold via an ether bond (**39** and **40**) had very meagre potency against resistant strains, regardless of the underlying resistance mechanism, showing, in this case, the attachment to the macrolide via ester bond to be more favourable.

In comparison to the clinically important macrolide antibiotics azithromycin and clarithromycin, the macrolones reported showed improved activity against macrolide resistant strains. However, compared to previously reported macrolones,[7–11] introduction of a cyclic structure within the aliphatic linker did not confer any great advantage to antibacterial potency, especially against cMLS *S. pyogenes*, where none of the compounds showed MIC below 8 μg/mL. Furthermore none of the compounds displayed activity against cMLS *S. aureus* strain which constitutively express the methyltransferase gene. It should be noted that the ketolides telithromycin and cethromycin are also inactive[36] against these strains.

3. Conclusion

In conclusion, structures characterized by the C–C bond at the position C-6 of the quinolone-3-carboxylic acid and central piperazine ring in the linker attached via ester/ether bond at C4″–OH to the macrolide scaffolds were prepared.

Compounds with a free 4-quinolone 3-carboxylic acid were antibacterially more potent than their ester counterparts. Attachment of linker to the 4″ position by an ester, rather than an ether bond, proved to be more favorable for antibacterial activity.

The most active compounds **20** and **26** exhibited improved potency against iMLSb and efflux resistant Gram-positive bacteria and *H. influenzae*.

4. Synthetic procedures

4.1. 1,1-Dimethylethyl 4-(2-propyn-1-yl)-1-piperazinecarboxylate (3)

To the degassed solution of piperazine-1-carboxylic acid *tert*-butyl ester **1** (1.0 g, 5.37 mmol) in acetonitrile (10 mL) were added Na_2CO_3 (1.71 g, 16.11 mmol) and mixture was stirred for 20 min. The suspension was heated to 50 °C and 3-bromo-propyne **2** (897.3 μL, 8.06 mmol) was added. The solvent was evaporated and the residue was extracted with EtOAc and water (2 × 50 mL). Organic layer was washed with NaCl and $NaHCO_3$ (2 × 50 mL). The organic layer was dried over K_2CO_3 and evaporated in vacuum yielding (0.97 g Y = 73%) oil product **3**.

MS(*m/z*): calcd for MH^+: 225.31, found: 225.12 (90.06%).

HRMS calcd for $C_{12}H_{21}N_2O_2$ $(M+H)^+$ 225.1603; found. 225.1594.

^{1}H NMR (500 MHz, DMSO) *δ*: 3.32 (4H, L_5, L_6-CH_2, ov), 3.29 (2H, L_{10}-CH_2, s), 3.17 (1H, L_{12}-CH, t), 2.38 (4H, L_7, L_8-CH_2), 1.39 (9H, L_1-CH_3).

^{13}C NMR (125 MHz, DMSO) *δ*: 154.17 (L_3-CO), 79.36 (L_2-C), 79.17 (L_{12}-CH), 76.29 (L_{11}-C), 51.25 (L_5, L_6, L_7, L_8-CH_2), 46.40 (L_{10}-CH_2), 28.41 (L_1-CH_3).

IR (KBr, cm^{-1}) 3300, 3243, 2976, 2932, 2859, 2814, 2761, 1689, 1456, 1419, 1365, 1298, 1244, 1168, 1121, 1085, 1006, 901.

4.3. Ethyl 6-[3-(4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-piperazinyl)-1-propyn-1-yl]-1-ethyl-4-oxo-1,4-dihydro-3-quinolinecarboxylate (7)

To the solution of ethyl 1-ethyl-6-iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylate **4** (0.5 g, 1.35 mmol) was dissolved in dry acetonitrile (13.5 mL) under N_2 at room temperature and copper(I) iodide (0.03 g, 0.14 mmol), triethylamine (6.6 mL, 47.10 mmol) and 1,1-dimethylethyl 4-(2-propyn-1-yl)-1-piperazinecarboxylate **3** (0.363 g, 1.617 mmol) were added. Reaction mixture stirred at room temperature for 20 min and heated to 50 °C and bis(triphenylphosphine)palladium (II) chloride (0.03 g, 0.04 mmol) was added. Reaction mixture stirred at 50 °C for 2 h. Solvent was evaporated and residue was diluted with EtOAc (10 mL) and water (10 mL). The aq layer was back extracted with EtOAc (2 × 10 mL). The organic was dried over K_2CO_3, and evaporated in vacuum yielding oil product (0.8 g).

The oil product (0.8 g) was added to a silica gel column and was eluted with DCM/MeOH/NH_4OH = 90/5/0.5. Collected fractions (0.50 g) were diluted with mixture of *n*-hexane/EtOAc 10/1 and product was filtered, washed with *n*-hexane/EtOAc 10/1 and dried to give crude product **7** (0.37 g, Y = 59%).

MS(*m/z*): calcd for MH^+: 467.57, found: 468.21 (98.81%).

HRMS calcd for $C_{26}H_{34}N_3O_5$ $(M+H)^+$ 468.2498; found 468.2492.

^{1}H NMR (500 MHz, DMSO) *δ*: 8.69 (1H, 2‴-H, s), 8.22 (1H, 5‴-H, d), 7.81 (1H, 8‴-H, d), 7.78 (1H, 7‴-H, dd), 4.,40 (2H, 11‴-CH_2, q), 4.23 (2H, 13‴-CH_2, q), 3.60 (2H, L_{10}-CH_2), 3.35 (4H, L_5, L_6-CH_2, ov), 2.50 (4H, L_7, L_8-CH_2, m), 1,40 (9H, L_1-CH_3, s), 1.36 (3H, 15‴-CH_3, t), 1.29 (3H, 14‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) *δ*: 172.38 (4‴-CO), 164.79 (12‴-CO), 154.24 (L_3-CO), 149.59 (2‴-CH), 138.58 (9‴-C), 135.40 (7‴-CH), 129.72 (5‴-CH), 128.60 (10‴-C), 119.08 (6‴-C), 118.35 (8‴-CH), 110.94 (3‴-C), 86.50 (L_{11}-C), 84.40 (L_{12}-C), 79. 22 (L_2-C), 60.20 (13‴-CH_2), 51.49 (L_5, L_6, L_7, L_8-CH_2), 48.39 (11‴-CH_2), 47.13 (L_{10}-CH_2), 28.42 (L_1-CH_3), 14.70 (15‴-CH_3), 14.67 (14‴-CH_3).

IR (KBr, cm^{-1}) 1980, 2931, 2798, 2762, 1722, 1695, 1631, 1606, 1589, 1544, 1489, 1457, 1417, 1365, 1342, 1314, 1297, 1247, 1233, 1165, 1123, 1086, 1053, 1005.

4.4. Ethyl 1-cyclopropyl-6-[3-(4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-piperazinyl)-1-propyn-1-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylate (8)

According to the procedure for synthesis of compound **7** was synthesized compound **8** starting from ethyl 1-cyclopropyl-6-iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylate **5** (2.0 g, 5.22 mmol) and 4-(2-propyn-1-yl)-1-piperazinecarboxylate **3** (1.4 g, 6.26 mmol). The oil product (1.8 g) was added to a silica gel column and was eluted with DCM/MeOH/NH_4OH = 90/5/0.5. Collected fractions (2.95 g) were diluted with mixture of *n*-hexane/EtOAc 10/1 and product was filtered, washed with *n*-hexane/EtOAc 10/1 and dried to give crude product **8** (2.83 g, Y = 98%).

MS(*m/z*): calcd for MH^+: 479.58, found: 480.19 (96.64%).

HRMS calcd for $C_{27}H_{33}N_3O_5$ $(M+H)^+$ 480.2484; found 480.2498.

^{1}H NMR (500 MHz, DMSO) *δ*: 8.48 (1H, 2‴-H, s), 8.17 (1H, 5‴-H, d), 8.06 (1H, 8‴-H, d), 7.83 (1H, 7‴-H, dd), 4.23 (2H, 13‴-CH_2, q), 3.66 (1H, 11‴-H, q), 3.60 (2H, L_{10}-CH_2, s), 3.37 (4H, L_5, L_6-CH_2, ov), 2.50 (4H, L_7, L_8-CH_2, m), 1.40 (9H, L_1-CH_3, s), 1.28 (3H, 14‴-CH_3, t), 1.23 (2H, 15‴-CH_2, dd), 1.10 (2H, 16‴-CH_2, dd).

^{13}C NMR (125 MHz, DMSO) *δ*: 172.46 (4‴-CO), 164.61 (12‴-CO), 154.25 (L_3-CO), 149.04 (2‴-CH), 140.45 (9‴-C), 135.29 (7‴-CH), 129.34 (5‴-CH), 127.95 (10‴-C), 119.30 (6‴-C), 118.67 (8‴-CH), 110.67 (3‴-C), 86.62 (L_{11}-C), 84.39 (L_{12}-C), 79. 20 (L2-C), 60.26 (13‴-CH_2), 51.51 (L_5, L_6, L_7, L_8-CH_2), 47.15 (L_{10}-CH_2), 35.13 (11‴-CH), 28.42 (L_2-CH_3), 14.66 (14‴-CH_3), 7.96 (15‴, 16‴-CH_2).

IR (KBr, cm^{-1}) 2977, 2933, 2813, 1728, 1691, 1637, 1597, 1545, 1486, 1455, 1421, 1365, 1346, 1318, 1245, 1173, 1128, 1088, 1034.

4.5. 6-[3-(4-{[(1,1-Dimethylethyl)oxy]carbonyl}-1-piperazinyl)-1-propyn-1-yl]-1-ethyl-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (9)

According to the procedure for synthesis of compound **7** compound **9**)was synthesized starting from 1-ethyl-6-iodo-4-oxo-1,

4-dihydro-3-quinolinecarboxylic acid **6** (0.49 g, 1.43 mmol) and 4-(2-propyn-1-yl)-1-piperazinecarboxylate **3** (0.45 g, 2.00 mmol) and isolated directly without column chromatography by dilution with mixture of *n*-hexane/EtOAc 10/1 and product was filtered, washed with *n*-hexane/EtOAc 10/1 and dried to give crude product **9** (0.75 g, Y = 88%).

MS(*m/z*): calcd for MH^+: 439.51, found: 440.20 (69.92%).

^{1}H NMR (500 MHz, DMSO) δ: 8.62 (1H, 2‴-H, s), 8.20 (1H, 5‴-H, d), 7.91 (1H, 8‴-H, d), 7.82 (1H, 7‴-H, dd), 4.40 (2H, 11‴-CH_2, q), 3.60 (2H, L_{10}-CH_2), 3.35 (4H, L_5, L_6-CH_2, ov), 2.50 (4H, L_7, L_8-CH_2, m), 1.40 (9H, L_1-CH_3, s), 1.36 (3H, 15‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ: 172.40 (4‴-CO), 166.81 (12‴-CO), 154.25 (L_3-CO), 149.38 (2‴-CH), 139.63 (9‴-C), 135.40 (7‴-CH), 129.35 (5‴-CH), 128.10 (10‴-C), 119.12 (6‴-C), 118.46 (8‴-CH), 110.80 (3‴-C), 86.55 (L_{11}-C), 84.41 (L_{12}-C), 79. 20 (L_2-C), 51.50 (L_5, L_6, L_7, L_8-CH_2), 48.40 (11‴-CH_2), 47.16 (L_{10}-CH_2), 28.42 (L_1-CH_3), 14.70 (15‴-CH_3).

4.6. Ethyl 1-ethyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylate (10)

To the solution of **7** (0.26 g, 0.56 mmol) in DCM (2.5 mL) was added CF_3COOH (2.5 mL, 0.024 mol). .Reaction mixture was stirred at rt for 2.5 h. To the reaction mixture were added DCM (10 mL) and water (10 mL). Layers were separated, water layer was extracted with DCM (2 × 10 mL) and to the water layer DCM (10 mL) was added and pH adjusted from 1.8 to 9.5 by addition of aq soln NH_4OH. Layers were separated; water layer was extracted with DCM (2 × 15 mL). The organic extract was dried (K_2CO_3) and concentrated under vacuum to afford title product **10** (0.17 g, Y = 82%) as yellow crystalline product.

MS(*m/z*): calcd for MH^+: 367.45, found: 368.15 (96.01%).

HRMS calcd for $C_{21}H_{25}N_3O_3$ $(M+H)^+$ 368.1974; found 368.1982.

^{1}H NMR (500 MHz, DMSO) δ: 8.69 (1H, 2‴-H, s), 8.22 (1H, 5‴-H, d), 7.82 (1H, 8‴-H, d), 7.78 (1H, 7‴-H, dd), 4.41 (2H, 11‴-CH_2, q), 4.23 (2H, 13‴-CH_2, q), 3.52 (2H, L_{10}-CH_2, s), 2.74 (4H, L_5, L_6-CH_2, ov), 2.48 (4H, L_7, L_8-CH_2, ov), 1.36 (3H, 15‴-CH_3, t), 1.29 (3H, 14‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ: 172.40 (4‴-CO), 164.81 (12‴-CO), 149.58 (2‴-CH), 138.51 (9‴-C), 135.36 (7‴-CH), 129.68 (5‴-CH), 128.61 (10‴-C), 119.28 (6‴-C), 118.33 (8‴-CH), 110.91 (3‴-C), 87.12 (L_{11}-C), 84.18 (L_{12}-C), 60.19 (13‴-CH_2), 52.81 (L_7, L_8-CH_2), 48.39 (11‴-CH_2), 47.76 (L_{10}-CH_2), 45.68 (L_5, L_6-CH_2), 14.71 (15‴-CH_3), 14.69 (14‴-CH_3).

IR (KBr, cm^{-1}) 2932, 2818, 1719, 1688, 1630, 1592, 1544, 1487, 1449, 1383, 1365, 1313, 1227, 1189, 1165, 1129, 1084, 1026, 953.

4.7. Ethyl 1-cyclopropyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylate (11)

Applying the same protocol as for the synthesis of compound **10**, compound **11** was obtained from the compound **8** (2.83 g, 5.90 mmol). Pure product **11** (0.66 g, Y = 28%) was obtained as white crystalline product.

MS(*m/z*): calcd for MH^+: 379.46, found: 380.14 (94.58%).

HRMS calcd for $C_{22}H_{25}N_3O_3$ $(M+H)^+$ 380.1974; found 380.1981.

^{1}H NMR (500 MHz, DMSO) δ: 8.48 (1H, 2‴-H, s), 8.17 (1H, 5‴-H, d), 8.06 (1H, 8‴-H, d), 7.83 (1H, 7‴-H, dd), 4.23 (2H, 13‴-CH_2, q), 3.66 (1H, 11‴-CH, q), 3.52 (2H, L10-CH_2, s), 2.73 (4H, L_5, L_6-CH_2, ov), 2.47 (4H, L_7, L_8-CH_2, ov), 1.28 (3H, 14‴-CH_3, t), 1.24 (2H, 15‴-CH_2, dd), 1.10 (2H, 16‴-CH_2, dd).

^{13}C NMR (125 MHz, DMSO) δ: 172.48 (4‴-CO), 164.62 (12‴-CO), 149.02 (2‴-CH), 140.37 (9‴-C), 135.25 (7‴-CH), 129.30 (5‴-CH), 127.94 (10‴-C), 119.51 (6‴-C), 118.65 (8‴-CH), 110.64 (3‴-C), 87.21 (L_{11}-C), 84.17 (L_{12}-C), 60.26 (13‴-CH_2), 53.06 (L_7, L_8-CH_2), 47.81 (L_{10}-CH_2), 45.82(L_5, L_6-CH_2), 35.13 (11‴-CH), 14.66 (14‴-CH_3), 7.95 (15‴, 16‴-CH_2).

IR (KBr, cm^{-1}) 2926, 2805, 1724, 1631, 1594, 1543, 1487, 1452, 1383, 1348, 1319, 1245, 1181, 1164, 1090, 1045, 1010, 929.

4.8. 1-Ethyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylic acid (12)

Applying the same protocol as for the synthesis of compound **10**, compound **12** was obtained from the compound **9** (0.75 g, 1.71 mmol). Pure product **12** (0.45 g, Y = 77%) was obtained as white crystalline product.

MS(*m/z*): calcd for MH^+: 39.39, found: 340.2 (67.92%).

^{1}H NMR (500 MHz, DMSO) δ: 8.60 (1H, 2‴-H, s), 8.18 (1H, 5‴-H, d), 7.86 (1H, 8‴-H, d), 7.82 (1H, 7‴-H, dd), 4.40 (2H, 11‴-CH_2, q), 3.52 (2H, L_{10}-CH_2), 2.74 (4H, L_5, L_6-CH_2, ov), 2.48 (4H, L_7, L_8-CH_2, m), 1.36 (3H, 15‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ: 172.40 (4‴-CO), 166.79 (12‴-CO), 149.54 (2‴-CH), 139.34 (9‴-C), 135.40 (7‴-CH), 129.59 (5‴-CH), 128.13 (10‴-C), 119.46 (6‴-C), 118.26 (8‴-CH), 110.70 (3‴-C), 87.21 (L_{11}-C), 84.18 (L_{12}-C), 53.09 (L_7, L_8-CH_2), 48.40 (11‴-CH_2), 45.76 (L_5, L_6-CH_2), 47.75 (L_{10}-CH_2), 14.70 (15‴-CH_3).

4.9. 4“-*O*-(3-{4-[3-(1-Ethyl-3-ethoxycarbonyl-1,4-dihydro-4-oxo-quinolyn-6-yl)prop-2-ynyl]piperazine-1-yl}propyonyl)-6-*O*-methyl-erythromycin A (16)

To the stirred solution of **13** (0.08 g, 0.10 mmol) in acetonitrile (4 mL) was added ethyl 1-ethyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylate **10** (0.15 g, 0.41 mmol), H_2O (0.1144 mL) and Et_3N (0.045 mL). Reaction mixture was stirred at 80 °C for 24 h and diluted with EtAc (10 mL) and poured into satd $NaHCO_3$ (10 mL). The organic phase was separated from aqueous phase and the aqueous phase extracted with EtAc (2 × 10 mL). The combined organic extracts were washed (brine), dried (K_2CO_3), filtered and the solvent removed under reduced pressure. The residue purified by low-pressure column chromatography in system of solvents and DCM/MeOH/NH_3 = 90/5/0.5; afterwards **16** (0.115 g, Y = 92%) as beige crystalline product.

MS(*m/z*): calcd for MH^+: 1169.45, found: 1169.63 (91.34%).

HRMS calcd for $C_{62}H_{97}N_4O_{17}$ $(M+H)^+$ 1169.6849; found. 1169.6902.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.60 (1H, 5‴-H, d), 8.49 (1H, 2‴-H, s), 7.70 (1H, 7‴-H, dd), 7.37 (1H, 8‴-H, dd), 5.07 (1H, 13-H, dd), 4.99 (1H, 1″-H, dd), 4.69 (1H, 4″-H, d), 4.59 (1H, 1′-H., d), 4.41 (2H, 13‴-CH_2, q), 4.35 (1H, 5″-H, dq), 4.25 (1H, 11‴-CH, q), 3.78 (1H, 3-H, ov), 3.77 (1H, 11-H, ov), 3.74 (1H, 5′-H, m), 3.65 (1H, 5-H, d), 3.53 (2H, L_{10}-CH_2, s), 3.31 (3H, 3″O-CH_3, s), 3.19 (1H, 2′-H, dd), 3.04 (3H, 6O-CH_3, s), 3.00 (1H, 10-H, dq), 2.90 (1H, 2-H, dq), 2.75 (2H, L_3-CH_2, ov), 2.68 (4H, L_7, L_8-CH_2, ov), 2.58 (1H, 8-H, m), 2.56 (1H, 3′-H, m), 2.55 (2H, L_2-CH_2, ov), 2.53 (4H, L_5, L_6-CH_2, ov), 2.41 (1H, 2″a-H, d), 2.32 (6H, 3′N-$(CH_3)_2$, s), 1.94 (1H, 4-H, m), 1.91 (1H, 14a-H, m), 1.84 (1H, 7a-H, dd), 1.70 (1H, 7b-H, dd), 1.66 (1H, 4'a-H, m), 1.63 (1H, 2″b-H, dd), 1.54 (3H, 15‴-CH_3, t), 1.48 (1H, 14b-H, m), 1.42 (3H, 14‴-CH_3, t), 1.38 (3H, 6-CH_3, s), 1.25 (1H, 4′b-H, ov), 1.22 (3H, 2-CH_3, d), 1.20 (3H, 5′-CH_3, d), 1.18 (3H, 5″-CH_3, d), 1.15 (3H, 3″-CH_3, s), 1.14 (3H, 8-CH_3, d), 1.13 (3H, 10-CH_3, d), 1.12 (3H, 12-CH_3, s), 1.11 (3H, 4-CH_3, d), 0.85 (3H, 15-CH_3, t).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 220.96 (9-*C*O), 175.63 (1-*C*O), 173.45 (4‴-*C*O), 171.80 (L_1-*C*O), 165.52 (12‴-*C*O), 148.47 (2‴-CH), 137.95 (9‴-C), 135.23 (7‴-CH), 131.50 (5‴-CH), 129.05 (10‴-C), 119.96 (6‴-C), 115.55 (8‴-CH), 111.48 (3‴-C), 101.97 (1′-CH), 95.91 (1″-CH), 85.78 (L_{11}-C), 84.04 (L_{12}-C), 80.35 (5-CH), 78.59 (4″-CH), 78.18 (3-CH), 77.90 (6-C), 76.49 (13-CH), 74.20 (12-C),

72.68 (3″-C), 70.95 (2′-CH), 69.00 (11-CH), 67.67 (5′-CH), 65.22 (3′-CH), 62.90 (5″-CH), 60.90 (13‴-CH_2), 53.31 (L_3-CH_2), 52.69 (L_2-CH_2), 51.96 (L_7, L_8-CH_2), 50.58 (6O-CH_3), 49.37 (3″O-CH_3), 48.82 (11‴-CH), 47.62 (L_{10}-CH_2), 45.24 (8-CH), 44.76 (2-CH), 40.13 (3'N-$(CH_3)_2$), 39.11 (7-CH_2), 38.69 (4-CH), 37.09 (10-CH), 35.10 (2″-CH_2), 32.40 (L_5, L_6-CH_2), 28.79 (4′-CH_2), 21.78 (5′-CH_3), 21.03 (3″-CH_3), 20.94 (14-CH_2), 19.60 (6-CH_3), 18.28 (5″-CH_3), 17.94 (8-CH_3), 15.89 (12-CH_3), 15.86 (2-CH_3), 14.42 (15‴,-CH_3), 14.34 (14‴-CH_3), 12.26 (10-CH_3), 10.50 (15-CH_3), 9.03 (4-CH_3).

IR (KBr, cm^{-1}) 2976, 2935, 2821, 1733, 1691, 1640, 1599, 1489, 1456, 1379, 1315, 1228, 1170, 1084, 1012, 807.

4.10. 4“-*O*-(3-{4-[3-(1-Cyclopropyl-3-etoxycarbonyl-1,4-dihydro-4-oxo-quinolin-6-yl)prop-2-ynyl]piperazine-1-il}propyonyl)-6-*O*-metil-erythromycin A (17)

Applying the same protocol as for the synthesis of compound **16**, compound **17** was obtained from the compound **13** (0.20 g, 0.25 mmol) and ethyl 1-cyclopropyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylate **11** (0.19 g, 0.50 mmol). Crude product was purified by low-pressure column chromatography in system of solvents and DCM/MeOH/NH_3 = 90/5/0.5; after warded **17** (0.12 g, Y = 37%) was obtained as white crystalline product.

MS(*m/z*): calcd for MH^+: 1181.48, found: 1181.63 (94.34%)

HRMS calcd for $C_{63}H_{97}N_4O_{17}$ $(M+H)^+$ 1181.6849; found 1181.6871

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.59 (1H, 2‴-H, s), 8.54 (1H, 5‴-H, d), 7.86 (1H, 8‴-H, dd), 7.71 (1H, 7‴-H, dd), 5.08 (1H, 13-H, dd), 5.00 (1H, 1″-H, dd), 4.69 (1H, 4″-H, d), 4.59 (1H, 1′-H., d), 4.40 (2H, 13‴-CH_2, q), 4.34 (1H, 5″-H, dq), 3.78 (1H, 3-H, ov), 3.77 (1H, 11-H, ov), 3.74 (1H, 5′-H, m), 3.66 (1H, 5-H, d), 3.54 (2H, L_{10}-CH_2, s), 3.48 (1H, 11‴-CH, m), 3.31 (3H, 3″O-CH_3, s), 3.18 (1H, 2′-H, dd), 3.04 (3H, 6O-CH_3, s), 3.00 (1H, 10-H, dq), 2.90 (1H, 2-H, dq), 2.75 (2H, L_3-CH_2, ov), 2.68 (4H, L_7, L_8-CH_2, ov), 2.59 (1H, 8-H, m), 2.56 (2H, L_2-CH_2, ov), 2.53 (4H, L_5, L_6-CH_2, ov), 2.52 (1H, 3'-H, m), 2.42 (1H, 2″a-H, d), 2.30 (6H, 3′N–$(CH_3)_2$, s), 1.95 (1H, 4-H, m), 1.91 (1H, 14a-H, m), 1.84 (1H, 7a-H, dd), 1.70 (1H, 7b-H, dd), 1.64 (1H, 4′a-H, m), 1.62 (1H, 2″b-H, dd), 1.49 (1H, 14b-H, m), 1.40 (3H, 14‴-CH_3, t), 1.38 (3H, 6-CH_3, s), 1.34 (2H, 15‴-CH_2, dq), 1.22 (1H, 4′b-H, ov), 1.21 (3H, 2-CH_3, d), 1.19 (3H, 5′-CH_3, d), 1.16 (3H, 5″-CH_3, d), 1.15 (3H, 3″-CH_3, s), 1.15 (2H, 16‴-CH_2, ov), 1.14 (3H, 8-CH_3, d), 1.13 (3H, 10-CH_3, d), 1.12 (3H, 12-CH_3, s), 1.11 (3H, 4-CH_3, d), 0.85 (3H, 15-CH_3, t).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 220.97 (9-*C*O), 175.63 (1-*C*O), 173.52 (4‴-*C*O), 171.81 (L_1-*C*O), 165.45 (12‴-*C*O), 148.51 (2‴-CH), 139.86 (9‴-C), 135.09 (7‴-CH), 131.03 (5‴-CH), 128.32 (10‴-C), 120.14 (6‴-C), 116.44 (8‴-CH), 111.37 (3‴-C), 102.01 (1′-CH), 95.91 (1″-CH), 85.76 (L_{11}-C), 84.09 (L_{12}-C), 80.35 (5-CH), 78.59 (4″-CH), 78.18 (3-CH), 77.90 (6-C), 76.68 (13-CH), 74.19 (12-C), 72.69 (3″-C), 70.96 (2′-CH), 69.00 (11-CH), 67.73 (5′-CH), 65.24 (3'-CH), 62.90 (5″-CH), 60.90 (13‴-CH_2), 53.34 (L_3-CH_2), 52.72 (L_2-CH_2), 52.02 (L_7, L_8-CH_2), 50.58 (6O*CH*$_3$), 49.36 (3″O*CH*$_3$), 47.62 (L_{10}-CH_2), 45.25 (8-CH), 44.77 (2-CH), 40.18 (3′N-(*CH*$_3$)$_2$), 39.12 (7-CH_2), 38.69 (4-CH), 37.09 (10-CH), 35.11 (2″-CH_2), 34.42 (11‴-CH), 32.45 (L_5, L_6-CH_2), 28.67 (4′-CH_2), 21.80 (5′-CH_3), 21.04
(3″-CH_3), 20.94 (14-CH_2), 19.61 (6-CH_3), 18.28 (5″-CH_3), 17.94 (8-CH_3), 15.89 (12-CH_3), 15.86 (2-CH_3), 14.34 (14‴-CH_3), 12.27 (10-CH_3), 10.50 (15-CH_3), 9.02 (4-CH_3), 8.14 (15‴, 16‴-CH_2).

IR (KBr, cm^{-1}) 3454, 2975, 2937, 2829, 1736, 1693, 1642, 1601, 1546, 1486, 1459, 1379, 1345, 1248, 1171, 1126, 1109, 1051, 1034, 1013.

4.11. 9-Deoxo-4“-*O*-(3-{4-[3-(1-ethyl-3-ethoxycyrbonyl-1,4-dihydro-4-oxo-quinolin-6-yl)prop-2-ynyl]piperazine-1-il}propyonyl)-9a,11-*O*-dimethyl-9a-aza-9a-homoerythromycin A (18)

Applying the same protocol as for the synthesis of compound **16**, compound **18** was obtained from the compound **14** (0.16 g, 0.16 mmol) and ethyl 1-ethyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylate **10** (0.17 g, 0.46 mmol). Crude product was purified by low-pressure column chromatography in system of solvents and DCM/MeOH/NH_3 = 90/5/0.5; after warded **18** (0.02 g, Y = 5%) was obtained as white crystalline product.

MS(*m/z*): calcd for MH^+: 1184.51, found: 1184.62 (70.60%)

HRMS calcd for $C_{63}H_{102}N_5O_{16}$ $(M+H)^+$ 1184.7322; found 1184.7361.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.56 (1H, 5‴-H, d), 8.48 (1H, 2‴-H, s), 7.69 (1H, 7‴-H, dd), 7.40 (1H, 8‴-H, d), 5.16 (1H, 1″-H, d), 4.69 (1H, 13-H, dd), 4.70 (1H, 4″-H, d), 4.58 (1H, 1′-H., d), 4.41 (2H, 13‴-CH_2, ov), 4.42 (1H, 5″-H, ov), 4.39 (1H, 3-H, ov), 4.25 (2H, 11‴-CH, q), 3.80 (1H, 5′-H, m), 3.62 (1H, 5-H, d), 3.59 (3H, 11O-CH_3, s), 3.53 (2H, L_{10}-CH_2, s), 3.40 (1H, 11-H, s), 3.32 (3H, 3″O-CH_3, s), 3.26 (1H, 2′-H, dd), 2.76 (2H, L_3-CH_2, ov), 2.76 (1H, 2-H, ov), 2.70 (1H, 10-H, ov), 2.68 (4H, L_7, L_8-CH_2, ov), 2.60 (1H, 3′-H, ov), 2.59 (2H, L_2-CH_2, ov), 2.54 (4H, L_5, L_6-CH_2, ov), 2.52 (1H, 9a-H, ov), 2.40 (1H, 2″a-H, d), 2.34 (6H, 3′N-$(CH_3)_2$, s), 2.25 (3H, 9 N-CH_3, s), 2.07 (1H, 9b-H, t), 2.01 (1H, 8-H, ov), 2.01 (1H, 4-H, ov), 1.92 (1H, 14a-H, m), 1.73 (1H, 7a-H, d), 1.68 (1H, 4′a-H, m), 1.61 (1H, 2″b-H, dd), 1.55 (3H, 15‴-CH_2, t), 1.47 (1H, 14b-H, m), 1.42 (3H, 14‴-CH_3, t), 1.32 (1H, 7b-H, ov), 1.27 (3H, 6-CH_3, s), 1.26 (1H, 4′b-H, ov), 1.22 (3H, 3″-CH_3, s), 1.19 (3H, 2-CH_3, d), 1.18 (3H, 5″-CH_3, d), 1.17 (3H, 5'-CH_3, d), 1.12 (3H, 12-CH_3, s), 1.03 (3H, 10-CH_3, d), 1.06 (3H, 4-CH_3, d), 0.91 (8-CH_3, d), 0.89 (15-CH_3, t).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.91 (1-*C*O), 173.45 (4‴-*C*O), 171.91 (L_1-*C*O), 165.56 (12‴-*C*O), 148.45 (2‴-CH), 137.92 (9‴-C), 135.29 (7‴-CH), 131.45 (5‴-CH), 129.04 (10‴-C), 119.99 (6‴-C), 115.56 (8‴-CH), 111.45 (3‴-C), 102.23 (1′-CH), 94.71 (1″-CH), 85.84(L_{11}-C), 84.01 (L_{12}-C), 83.41 (5-CH), 78.87 (4″-CH), 77.99 (3-CH), 77.71 (13-CH), 84.94 (11-CH), 73.06 (6-C), 74.30 (12-C), 73.10 (3″-C), 70.91 (2′-CH), 70.91 (9-CH_2), 67.64 (5′-CH), 65.40 (3′-CH), 62.71 (5″-CH), 62.56 (10-CH), 62.06 (11O-CH_3), 60.89 (13‴-CH_2), 53.33 (L_3-CH_2), 52.64 (L_2-CH_2), 51.97 (L_7, L_8-CH_2), 49.36 (3″O*CH*$_3$), 48.82 (11‴-CH), 47.58 (L_{10}-CH_2), 45.36 (2-CH), 42.57 (7-CH_2), 42.62 (4-CH), 40.22 (3′N-(*CH*$_3$)$_2$), 35.82 (9N–CH_3), 34.99 (2″-CH_2), 32.36 (L_5, L_6-CH_2), 29.17 (4′-CH_2), 27.56 (6-CH_3), 26.62 (8-CH), 22.11 (8-CH_3), 21.73 (3″-CH_3), 21.65 (14-CH_2), 21.24 (5′-CH_3), 17.64 (5″-CH_3), 16.98 (12-CH_3), 14.58 (2-CH_3), 14.42 (15‴-CH_2), 14.34 (14‴-CH_3), 11.18 (15-CH_3), 9.16 (4-CH_3), 7.09 (10-CH_3).

IR (KBr, cm^{-1}) 2974, 2935, 2825, 1732, 1693, 1639, 1599, 1489, 1455, 1380, 1315, 1228, 1167, 1128, 1092, 1079, 1051, 1014, 985, 959, 807.

4.12. 9-Deoxo-4“-*O*-(3-{4-[3-(1-cycloprpyl-3-ethoxycarbonyl-1,4-dihydro-4-oxo-quinolin-6-yl)prop-2-ynyl]piperazine-1-il}propyonyl)-9a,11-*O*-dimethyl-9a-aza-9a-homoerythromycin A (19)

Applying the same protocol as for the synthesis of compound **16**, compound **19** was obtained from the compound **14** (0.20 g, 0.20 mmol) and ethyl 1-cyclopropyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylate **11** (0.15 g, 0.40 mmol) and formed product was 2′Oac derivate that was dissolved in methanol (50 mL) and reaction mixture was stirred

at50 °C over night. Crude product was purified by low-pressure column chromatography in system of solvents and DCM/MeOH/NH_3 = 90:5:0.5; after warded **19** (0.03 g, Y = 6%) was obtained as white crystalline product.

MS(*m/z*): calcd for MH^+: 1196.54, found: 1196.62 (84.35%).

HRMS calcd for $C_{64}H_{102}N_5O_{16}$ $(M+H)^+$ 1196.7322; found 1196.7361.

^{1}H NMR (500 MHz, $CDCl_3$) δ**:** 8.58 (1H, 2‴-H, s), 8.54 (1H, 5‴-H, d), 7.86 (1H, 8‴-H, d), 7.70 (1H, 7‴-H, dd), 5.17 (1H, 1″-H, d), 4.69 (1H, 13-H, dd), 4.70 (1H, 4″-H, d), 4.58 (1H, 1′-H., d), 4.40 (2H, 13‴-CH_2, ov), 4.44 (1H, 5″-H, ov), 4.38 (1H, 3-H, ov), 3.80 (1H, 5′-H, m), 3.63 (1H, 5-H, d), 3.59 (3H, 11O-CH_3, s), 3.53 (2H, L_{10}-CH_2, s), 3.47 (2H, 11‴-CH, m), 3.41 (1H, 11-H, s), 3.33(3H, 3″O-CH_3, s), 3.26 (1H, 2'-H, dd), 2.75 (1H, 2-H, ov), 2.72 (2H, L_3-CH_2, ov), 2.69 (1H, 10-H, ov), 2.68 (4H, L_7, L_8-CH_2, ov), 2.59 (1H, 3′-H, ov), 2.55 (2H, L_2-CH_2, ov), 2.54 (4H, L_5, L_6-CH_2, ov), 2.53(1H, 9a-H, ov), 2.40 (1H, 2″a-H, d), 2.32 (6H, 3′N-$(CH_3)_2$, s), 2.25 (3H, 9N–CH_3, s), 2.09 (1H, 9b-H, t), 2.02 (1H, 4-H, ov), 1.96 (1H, 8-H, ov), 1.93 (1H, 14a-H, m), 1.74 (1H, 7a-H, d), 1.68 (1H, 4′a-H, m), 1.61 (1H, 2″b-H, dd), 1.35 (3H, 15‴-CH_2, dq), 1.48 (1H, 14b-H, m), 1.42 (3H, 14‴-CH_3, t), 1.31 (1H, 7b-H, ov), 1.27 (3H, 6-CH_3, s), 1.26 (1H, 4′b-H, ov), 1.21 (3H, 3″-CH_3, s), 1.20 (3H, 2-CH_3, d), 1.17 (3H, 5″-CH_3, d), 1.15 (3H, 5′-CH_3, d), 1.13 (3H, 12-CH_3, s), 1.13 (2H, 16‴-CH_2, dq), 1.07 (3H, 4-CH_3, d), 1.04 (3H, 10-CH_3, d), 0.91 (8-CH_3, d), 0.89 (15-CH_3, t).

^{13}C NMR (125 MHz, $CDCl_3$) δ**:** 177.92 (1-*C*O), 173.52 (4‴-*C*O), 171.92 (L_1-*C*O), 165.49 (12‴-*C*O), 148.49 (2‴-CH), 139.85 (9‴-C), 135.15 (7‴-CH), 130.99 (5‴-CH), 128.32 (10‴-C), 120.18 (6‴-C), 116.44 (8‴-CH), 111.36 (3‴-C), 102.29 (1′-CH), 94.72 (1″-CH), 85.82(L_{11}-C), 84.95 (11-CH), 84.08 (L_{12}-C), 83.43 (5-CH), 78.88 (4″-CH), 78.00 (3-CH), 77.72 (13-CH), 73.07 (6-C), 74.31(12-C), 73.11 (3″-C), 70.92 (2′-CH), 70.92 (9-CH_2), 67.71 (5′-CH), 65.43 (3′-CH), 62.72 (5″-CH), 62.57 (10-CH), 62.07 (11O-CH_3), 60.90 (13‴-CH_2), 53.36 (L_3-CH_2), 52.68 (L_2-CH_2), 52.03 (L_7, L_8-CH_2), 49.36 (3″O*C*H_3), 47.62 (L_{10}-CH_2), 45.37 (2-CH), 42.59 (7-CH_2), 42.64 (4-CH), 40.26 (3′N–(*C*H_3)$_2$), 35.83 (9N–CH_3), 35.01 (2″-CH_2), 34.41 (11‴-CH), 32.41 (L_5, L_6-CH_2), 29.01 (4'-CH_2), 27.57 (6-CH_3), 26.63 (8-CH), 22.12 (8-CH_3), 21.75(3″-CH_3), 21.66 (14-CH_2), 21.26 (5′-CH_3), 17.64 (5″-CH_3), 16.98 (12-CH_3), 14.58 (2-CH_3), 14.33 (14‴-CH_3), 11.19 (15-CH_3), 9.15 (4-CH_3), 8.13 (15‴-CH_2), 8.13 (16‴-CH_2), 7.09 (10-CH_3).

IR (KBr, cm^{-1}) 2984, 2936, 2824, 1733, 1693, 1642, 1600, 1546, 1600, 1485, 1456, 1379, 1345, 1327, 1318, 1247, 1166, 1128, 1077, 1014, 960, 918.

4.13. 9-Deoxo-4"-*O*-(3-{4-[3-(1-ethyl-3-carboxy-1,4-ihydro-4-oxo-quinolin-6-yl)prop-2-ynyl]piperazine-1-yl}propyonyl)-9a,11-O-dimethyl-9a-aza-9a-homoerythromycin A (20)

Applying the same protocol as for the synthesis of compound **16**, compound **20** was obtained from the compound **14** (0.20 g, 0.20 mmol) and 1-Etil-1,4-dihidro-4-okso-6-[3-(1-piperazinil)-1-propin-1-il]-3-kinolinkarboksilna kiselina **12** (0.45 g, 1.33 mmol) and formed product was 2′Oac derivate that was dissolved in methanol (50 mL) and reaction mixture was stirred at 50 °C over night. Crude product was purified by low-pressure column chromatography in system of solvents and DCM/MeOH/NH_3 = 90/5/0.5; after warded **19** (0.09 g, Y = 6%) was obtained as white crystalline product.

MS(*m/z*): calcd for MH^+: 1156.46, found: 1156.54 (92.46%).

HRMS calcd for $C_{61}H_{98}N_5O_{16}$ $(M+H)^+$ 1156.4638; found. 1156.4662.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.77 (1H, 2‴-H, s), .59 (1H 5‴-H, d), 7.85 (1H, 7‴-H, dd), 7.60 (1H, 8‴-H, d), 5.16 (1H, 1″-H, d), 4.75 (1H, 4″-H, d), 4.68 (1H, 13-H, dd), 4.60 (1H, 1′-H., d), 4.42 (1H, 5″-H, ov), 4.39 (2H, 11‴-CH_2, ov), 4.37 (1H, 3-H, ov), 3.88 (1H, 5′-H, m), 3.63 (1H, 5-H, d), 3.58 (3H, 11O-CH_3, s), 3.55 (2H, L_{10}-CH_2, s), 3.40 (1H, 11-H, s), 3.32 (3H, 3″O-CH_3, s), 3.29 (1H, 2″a-H, d), 2.24 (3H, 9N-CH_3, s), 2.05 (1H, 9b-H, ov), 2.02 (1H, 8-H, ov), 2.01 (1H, 4-H, ov), 1.92 (1H, 14a-H, m), 1.73 (1H, 7a-H, d), 1.60 (1H, 2″b-H, ov), 1.60 (3H, 15‴-CH_2, t), 1.46 (1H, 14b-H, m), 1.33 (1H, 7b-H, ov), 1.27 (1H, 4′b-H, ov), 1.25 (3H, 6-CH_3, s), 1.21 (3H, 5′-CH_3, d), 1.18 (3H, 2-CH_3, d), 1.15 (3H, 5″-CH_3, d), 1.14 (3H, 3″-CH_3, s), 1.11 (3H, 12-CH_3, s), 1.05 (3H, 10-CH_3, ov), 1.02 (3H, 4-CH_3, ov), 0.92 (8-CH_3, ov), 0.88 (15-CH_3, ov).

^{13}C NMR (125 MHz, DMSO) δ**:** 177.91 (4‴-*C*O), 177.88 (1-*C*O), 172.06 (L_1-*C*O), 166.81 (12‴-*C*O), 147.98 (2‴-CH), 138.35 (9‴-C), 136.78 (7‴-CH), 130.64 (5‴-CH), 126.59 (10‴-C), 121.57 (6‴-C), 116.45 (8‴-CH), 109.39 (3‴-C), 102.00 (1′-CH), 94.79 (1″-CH), 87.41(L_{11}-C), 85.01 (11-CH), 83.77 (5-CH), 83.47 (L_{12}-C), 78.96 (4″-CH), 78.01 (3-CH), 77.88 (13-CH), 74.42 (12-C), 73.25 (6-C), 73.09 (3″-C), 71.09 (2′-CH), 70.96 (9-CH_2), 67.57 (5′-CH), 65.52 (3′-CH), 62.81 (5″-CH), 62.70 (10-CH), 62.13 (11O-CH_3), 53.42 (L_3-CH_2), 52.82 (L_2-CH_2), 52.05 (L_7, L_8-CH_2), 49.80 (11‴-CH), 49.46 (3″O*C*H_3), 47.64 (L_{10}-CH_2), 45.44 (2-CH), 42.78 (7-CH_2), 42.56 (4-CH), 35.82 (9N-CH_3), 34.99 (2″-CH_2), 32.74 (L_5, L_6-CH_2), 29.70 (4′-CH_2), 27.67 (6-CH_3), 26.75 (8-CH), 22.23 (8-CH_3), 21.77 (14-CH_2), 21.70 (5′-CH_3), 21.35 (3″-CH_3), 17.75 (5″-CH_3), 17.09 (12-CH_3), 14.70 (2-CH_3), 14.65 (15‴-CH_2), 11.30 (15-CH_3), 9.45 (4-CH_3), 7.25 (10-CH_3).

4.14. 9-Deoxo-4"-*O*-(3-{4-[3-(1-ethyl-3-ethxycarbonyl-1,4-ihydro-4-oxo-quinolin-6-yl)prop-2-ynyl]piperazine-1-yl}propyonyl)-9a-methyl-9a-aza-9a-homoerythromycin A (21)

Applying the same protocol as for the synthesis of compound **16**, compound **21** was obtained from the compound **15** (0.49 g, 0.61 mmol) and Ethyl 1-ethyl-4-oxo-6-[3-(1-piperazinyl)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylate **10** (0.90 g, 2.45 mmol). Crude product was purified by low-pressure column chromatography in system of solvents and DCM/MeOH/NH_3 = 90:5:0.5; after warded **21** (0.29 g, Y = 40%) was obtained as white crystalline product.

MS(*m/z*): calcd for MH^+: 1170.50, found: 1170.63 (72.54%).

HRMS calcd for $C_{62}H_{100}N_5O_{16}$ $(M+H)^+$ 1170.7165; found 1170.7236.

^{1}H NMR (500 MHz, $CDCl_3$) δ**:** 8.59 (1H, 5‴-H, d), 8.49 (1H, 2‴-H, s), 7.69 (1H, 7‴-H, dd), 7.41 (1H, 8‴-H, d), 5.20 (1H, 1″-H, dd), 4.71 (1H, 13-H, ov), 4.71 (1H, 4″-H, ov), 4.57 (1H, 1′-H., d), 4.42 (2H, 13‴-CH_2, q), 4.25 (1H, 3-H, ov), 4.25 (2H, 11‴-CH, q), 3.81 (1H, 5″-H, m), 3.70 (1H, 11-H, s), 3.66 (1H, 5′-H, ov), 3.63 (1H, 5-H, d), 3.54 (2H, L_{10}-CH_2, s), 3.32 (3H, 3″O-CH_3, s), 3.23 (1H, 2′-H, dd), 2.76 (1H, 2-H, ov), 2.71 (1H, 10-H, ov), 2.75 (2H, L_3-CH_2, ov), 2.68 (4H, L_7, L_8-CH_2, ov), 2.56 (2H, L_2-CH_2, ov), 2.55 (4H, L_5, L_6-CH_2, ov), 2.55 (1H, 3′-H, ov), 2.55 (1H, 9a-H, ov), 2.39 (1H, 2″a-H, d), 2.32 (3H, 9N-CH_3, s), 2.31 (6H, 3′N-$(CH_3)_2$, s), 2.07 (1H, 9b-H, ov), 2.04 (1H, 8-H, ov), 2.01 (1H, 4-H, ov), 1.91 (1H, 14a-H, m), 1.78 (1H, 7a-H, d), 1.68 (1H, 4′a-H, m), 1.61 (1H, 2″b-H, dd), 1.47 (1H, 14b-H, m), 1.55 (3H, 14‴-CH_3, t), 1.31 (3H, 6-CH_3, s), 1.42 (3H, 15‴-CH_2, dq), 1.29 (1H, 7b-H, ov), 1.26 (1H, 4′b-H, ov), 1.21 (3H, 2-CH_3, ov), 1.19 (3H, 5″-CH_3, ov), 1.14 (3H, 5′-CH_3, ov), 1.15 (3H, 3″-CH_3, ov), 1.11 (3H, 12-CH_3, ov), 1.09 (3H, 10-CH_3, d), 1.06 (3H, 4-CH_3, d), 0.91 (8-CH_3, ov), 0.89 (15-CH_3, ov).

^{13}C NMR (125 MHz, $CDCl_3$) δ**:** 178.84 (1-*C*O), 173.45 (4‴-*C*O), 171.91 (L_1-*C*O), 165.58 (12‴-*C*O), 148.45 (2‴-CH), 137.94 (9‴-C), 135.28 (7‴-CH), 131.47 (5‴-CH), 129.60 (10‴-C), 120.00 (6‴-C), 115.57 (8‴-CH), 111.47 (3‴-C), 102.25 (1′-CH), 94.56 (1″-CH), 85.84(L_{11}-C), 84.02 (L_{12}-C), 83.09 (5-CH), 78.72 (4″-CH), 77.59 (3-CH), 77.33 (13-CH), 74.15 (11-CH), 73.53 (6-C), 73.50 (12-C), 72.94 (3″-C), 70.81 (2′-CH), 70.00 (9-CH_2), 68.24 (5′-CH), 67.73 (5″-CH), 65.56 (3′-CH), 62.42 (10-CH), 60.90 (13‴-CH_2), 53.34 (L_3-

CH_2), 52.68 (L_2-CH_2), 51.99 (L_7, L_8-CH_2), 49.32 (3″OCH_3), 48.82 (11‴-CH), 47.60 (L_{10}-CH_2), 45.09 (2-CH), 42.10 (7-CH_2), 42.10 (4-CH), 40.24 (3′N-(CH_3)$_2$), 36.15 (9N-CH_3), 34.86 (2″-CH_2), 32.38 (L_5, L_6-CH_2), 28.79 (4′-CH_2), 27.46 (6-CH_3), 26.69 (8-CH), 22.77 (5′-CH_3), 21.86 (8-CH_3), 21.21 (3″-CH_3), 21.36 (14-CH_2), 17.73 (5″-CH_3), 16.09 (12-CH_3), 14.43 (2-CH_3), 14.43 (14‴-CH_3), 14.34 (15‴-CH_2), 11.18 (15-CH_3), 8.93 (4-CH_3), 7.26 (10-CH_3).

IR (KBr, cm^{-1}) 2972, 2933, 2822, 1732, 1692, 1639, 1599, 1489, 1456, 1379, 1315, 1230, 1168, 1094, 1048, 1014, 959, 903, 807.

4.15. 4“-*O*-(3-{4-[3-(1-Ethyl-3-ethoxycarbonyl-1,4-dihydro-4-oxo-quinolin-6-yl)propyl]piperazine-1-yl}propyonyl)-6-*O*-methyl-erythromycin A (22)

Hydrogenation of compound **16** (0.10 g, 0.09 mmol) in methnol (30.0 mL) over 10% Pd–C (0.03 g) at hydrogen pressure 5.0 bars for 20 h afforded after filtration of the catalyst and evaporation of organic solvent product **22** (0.05 g, Y = 36%) as white crystalline product.

MS(*m/z*): calcd for MH^+: 1173.48, found: 1173.82 (73.95%).

HRMS calcd for $C_{62}H_{101}N_4O_{17}$ $(M+H)^+$ 1173.7162; found 1173.7130.

^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.51 (1H, 2‴-H, s), 8.35 (1H, 5‴-H, d), 7.54 (1H, 7‴-H, dd), 7.41 (1H, 8‴-H, dd), 5.07 (1H, 13-H, dd), 4.99 (1H, 1″-H, dd), 4.69 (1H, 4″-H, d), 4.61 (1H, 1′-H., d), 4.41 (2H, 13‴-CH_2, q), 4.33 (1H, 5″-H, dq), 4.27 (1H, 11‴-CH, q), 3.76 (1H, 3-H, ov), 3.76 (1H, 11-H, ov), 3.78 (1H, 5′-H, m), 3.65 (1H, 5-H, ov), 3.31 (3H, 3″O-CH_3, s), 3.28 (1H, 2′-H, ov), 3.03 (3H, 6O-CH_3, s), 3.00 (1H, 10-H, ov), 2.92 (1H, 2-H, dq), 2.78 (2H, L_{12}-CH_2, ov), 2.75 (2H, L_3-CH_2, ov), 2.60 (4H, L_7, L_8-CH_2, ov), 2.59 (1H, 8-H, ov), 2.56 (4H, L_5, L_6-CH_2, ov), 2.55 (2H, L_2-CH_2, ov), 2.48 (1H, 3′-H, m), 2.48 (6H, 3′N-(CH_3)$_2$, s), 2.45 (2H, L_{10}-CH_2, ov), 2.41 (1H, 2″a-H, d), 1.95 (1H, 4-H, ov), 1.93 (2H, L_{11}-CH_2, ov)1.90 (1H, 14a-H, ov), 1.84 (1H, 7a-H, ov), 1.81 (1H, 4′a-H, ov), 1.67 (1H, 7b-H, ov), 1.63 (1H, 2″b-H, ov), 1.49 (1H, 14b-H, m), 1.41 (3H, 14‴-CH_3, t), 1.38 (3H, 6-CH_3, s), 1.55 (3H, 15‴-CH_3, t), 1.28 (1H, 4′b-H, ov), 1.22 (3H, 2-CH_3, d), 1.20 (3H, 5′-CH_3, d), 1.14 (3H, 5″-CH_3, ov), 1.15 (3H, 3″-CH_3, ov), 1.14 (3H, 8-CH_3, ov), 1.13 (3H, 10-CH_3, ov), 1.12 (3H, 12-CH_3, ov), 1.11 (3H, 4-CH_3, ov), 0.85 (3H, 15-CH_3, t).

^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 220.95 (9-*C*O), 175.64 (1-*C*O), 174.33 (4‴_*C*O), 171.64 (L_1-*C*O), 165.52 (12‴-*C*O), 148.14 (2‴-CH), 138.76 (6‴-C), 136.90 (9‴-C), 133.15 (7‴-CH), 127.06 (5‴-CH), 129.15 (10‴-C), 115.62 (8‴-CH), 110.75 (3‴-C), 101.71 (1′-CH), 95.90 (1″-CH), 80.46 (5-CH), 78.63 (4″-CH), 78.16 (6-C), 77.95 (3-CH), 76.55 (13-CH), 74.20 (12-C), 72.71 (3″-C), 70.85 (2′-CH), 69.01 (11-CH), 67.24 (5′-CH), 65.16 (3′-CH), 62.87 (5″-CH), 60.79 (13‴-CH_2), 57.07 (L_{10}-CH_2), 53.01 (L_3-CH_2), 52.25 (L_2-CH_2), 51.95 (L_7, L_8-CH_2), 50.59 (6O-CH_3), 49.41 (3″O-CH_3), 48.79 (11‴-CH), 45.19 (8-CH), 44.75 (2-CH), 39.94 (3′N-(CH_3)$_2$), 39.10 (7-CH_2), 38.71 (4-CH), 37.13 (10-CH), 35.08 (2″-CH_2), 32.77 (L_{12}-C), 31.90 (L_5, L_6-CH_2), 28.79 (4′-CH_2), 27.37 (L_{11}-C), 21.62 (5′-CH_3), 21.04 (3″-CH_3), 20.93 (14-CH_2), 19.63 (6-CH_3), 18.27 (5″-CH_3), 17.94
(8-CH_3), 15.88 (12-CH_3), 15.88 (2-CH_3), 14.50 (15‴-CH_3), 14.35 (14‴-CH_3), 12.25 (10-CH_3), 10.49 (15-CH_3), 9.17 (4-CH_3).

IR (KBr, cm^{-1}) 2969, 2936, 2883, 2826, 1731, 1687, 1609, 1494, 1455, 1377, 1315, 1227, 1166, 1083, 1012, 808.

4.16. 4“-*O*-(3-{4-[3-(1-Cyclopropyl-3-ethoxycarbonyl-1,4-dihyydro-4-oxo-quinolin-6-l)propyl]piperazine-1-yl}propyonyl)-6-*O*-methyl-erythromycin A (23)

Applying the same protocol as for the synthesis of compound **22**, compound **23** was obtained from **17** (0.09 g, 0.08 mmol) after filtration of the catalyst and evaporation of organic solvent product **23** (0.05 g, Y = 50%) as white crystalline product.

MS(*m/z*): calcd for MH^+: 1185.49, found: 1185.77 (90.75%).

HRMS calcd for $C_{63}H_{101}N_4O_{17}$ $(M+H)^+$ 1185.7162; found 1185.7205.

^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.60 (1H, 2‴-H, s), 8.29 (1H, 5‴-H, d), 7.86 (1H, 8‴-H, dd), 7.54 (1H, 7‴-H, dd), 5.06 (1H, 13-H, dd), 4.98 (1H, 1″-H, dd), 4.68 (1H, 4″-H, d), 4.60 (1H, 1′-H., d), 4.39 (2H, 13‴-CH_2, q), 4.31 (1H, 5″-H, dq), 3.77 (1H, 3-H, ov), 3.77 (1H, 11-H, ov), 3.75 (1H, 5′-H, m), 3.64 (1H, 5-H, ov), 3.47 (1H, 11‴-CH, m), 3.32 (3H, 3″O-CH_3, s), 3.30 (1H, 2′-H, ov), 3.03 (3H, 6O-CH_3, s), 3.00 (1H, 10-H, ov), 2.94 (1H, 2-H, ov), 2.91 (1H, 3′-H, m), 2.77 (2H, L_{12}-CH_2, ov), 2.77 (2H, L_3-CH_2, ov), 2.64 (4H, L_7, L_8-CH_2, ov), 2.60 (2H, L_2-CH_2, ov), 2.59 (1H, 8-H, ov), 2.55 (4H, L_5, L_6-CH_2, ov), 2.54 (6H, 3′N-(CH_3)$_2$, s), 2.50 (2H, L_{10}-CH_2, ov), 2.42 (1H, 2″a-H, d), 1.94 (1H, 4-H, ov), 1.92 (1H, 14a-H, ov), 1.88 (2H, L_{11}-CH_2, ov), 1.83 (1H, 4′a-H, ov), 1.80 (1H, 7a-H, ov), 1.67 (1H, 7b-H, ov), 1.63 (1H, 2″b-H, ov), 1.49 (1H, 14b-H, m), 1.41 (3H, 14‴-CH_3, t), 1.37 (3H, 6-CH_3, s), 1.33 (3H, 15‴-CH_3, dq), 1.30 (1H, 4′b-H, ov), 1.22 (3H, 5′-CH_3, ov), 1.20 (3H, 2-CH_3, ov), 1.13 (3H, 5″-CH_3, ov), 1.13 (3H, 3″-CH_3, ov), 1.13 (3H, 8-CH_3, ov), 1.13 (3H, 10-CH_3, ov), 1.13 (2H, 16‴-CH_2, ov), 1.12 (3H, 12-CH_3, ov), 1.10 (3H, 4-CH_3, ov), 0.84 (3H, 15-CH_3, t).

^{13}C NMR (125 MHz, DMSO) *δ*: 220.95 (9-*C*O), 175.66 (1-*C*O), 174.45 (4‴_*C*O), 171.55 (L_1-*C*O), 165.70 (12‴-*C*O), 148.17 (2‴-CH), 138.85 (9‴-C), 138.75 (6‴-C), 133.00 (7‴-CH), 128.38 (10‴-C), 126.54 (5‴-CH), 116.56 (8‴-CH), 110.66 (3‴-C), 101.62 (1′-CH), 95.89 (1″-CH), 80.44 (5-CH), 78.64 (4″-CH), 78.15 (6-C), 77.98 (3-CH), 76.69 (13-CH), 74.20 (12-C), 72.72 (3″-C), 70.74 (2′-CH), 69.01 (11-CH), 67.05 (5′-CH), 65.17 (3′-CH), 62.85 (5″-CH), 60.79 (13‴-CH_2), 56.91 (L_{10}-CH_2), 52.88 (L_3-CH_2), 52.00 (L_2-CH_2), 51.65 (L_7, L_8-CH_2), 50.58 (6O-CH_3), 49.44 (3″O-CH_3), 45.18 (8-CH), 44.74 (2-CH), 39.77 (3′N-(CH_3)$_2$), 39.08 (7-CH_2), 38.73 (4-CH), 37.13 (10-CH), 35.06 (2″-CH_2), 34.43 (11‴-CH), 32.75 (L_{12}-C), 31.72 (L_5, L_6-CH_2), 30.04 (4′-CH_2), 27.12 (L_{11}-C), 21.58 (5′-CH_3), 21.03 (3″-CH_3), 20.92 (14-CH_2), 19.64 (6-CH_3), 18.27 (5″-CH_3), 17.94 (8-CH_3), 15.88 (12-CH_3), 15.88 (2-CH_3), 14.34 (14‴-CH_3), 12.25 (10-CH_3), 10.49 (15-CH_3), 9.19 (4-CH_3), 8.04 (15‴-CH_3), 8.04 (16‴-CH_3).

IR (KBr, cm^{-1}) 2972, 2940, 2830, 1732, 1691, 1610, 1489, 1457, 1457, 1376, 1349, 1246, 1171, 1084, 1012, 985, 959, 891.

4.17. 9-Deoxo-4″-*O*-(3-{4-[3-(1-tyl-3-ethoxycarbonyl-1,4-ihydro-4-oxo-quinolin-6-yl)proypl]piperazine-1-yl}propyonyl)-9a,11-O-dimethyl-9a-aza-9a-homoerythromycin A (24)

Applying the same protocol as for the synthesis of compound **22**, compound **24** was obtained from **18** (0.05 g, 0.04 mmol) after filtration of the catalyst and evaporation of organic solvent product **24** (0.01 g, Y = 12%) as white crystalline product.

MS(*m/z*): calcd for MH^+: 1188.54, found: 1188.77 (70.42%).

HRMS calcd for $C_{63}H_{106}N_5O_{16}$ $(M+H)^+$ 1188.7635; found 1188.7672.

^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 8.49 (1H, 2‴-H, s), 8.35 (1H, 5‴-H, d), 7.52 (1H, 7‴-H, dd), 7.38 (1H, 8‴-H, d), 5.16 (1H, 1″-H, d), 4.70 (1H, 4″-H, d), 4.69 (1H, 13-H, dd), 4.58 (1H, 1′-H., d), 4.42 (1H, 5″-H, ov), 4.40 (2H, 13‴-CH_2, ov), 4.39 (1H, 3-H, ov), 4.25 (2H, 11‴-CH, q), 3.78 (1H, 5′-H, m), 3.62 (1H, 5-H, d), 3.59 (3H, 11O-CH_3, s), 3.41 (1H, 11-H, s), 3.32 (3H, 3″O-CH_3, s), 3.25 (1H, 2′-H, dd), 2.77 (2H, L_{12}-CH_2, ov), 2.75 (1H, 2-H, ov), 2.70 (2H, L_2-CH_2, ov), 2.67 (1H, 10-H, ov), 2.57 (1H, 3′-H, ov), 2.53 (4H, L_5, L_6-CH_2, ov), 2.51 (2H, L_3-CH_2, ov), 2.51 (4H, L_7, L_8-CH_2, ov), 2.50 (1H, 9a-H, ov), 2.40 (1H, 2″a-H, d), 2.35 (2H, L_{10}-CH_2, t), 2.30 (6H, 3′N-(CH_3)$_2$, s), 2.24 (3H, 9N-CH_3, s), 2.07 (1H, 9b-H, t), 2.01 (1H, 8-H, ov), 2.01 (1H, 4-H, ov), 1.92 (1H, 14a-H, m), 1.85 (2H, L_{11}-CH_2, ov), 1.75 (1H, 7a-H, d), 1.66 (1H, 4′a-H, m), 1.61 (1H, 2″b-H, dd), 1.55 (3H,

15‴-CH_2, t), 1.47 (1H, 14b-H, m), 1.42 (3H, 14‴-CH_3, t), 1.32 (1H, 7b-H, ov), 1.27 (1H, 4′b-H, ov), 1.26 (3H, 6-CH_3, s), 1.20 (3H, 3″-CH_3, s), 1.19 (3H, 2-CH_3, d), 1.16 (3H, 5″-CH_3, d), 1.12 (3H, 5′-CH_3, d), 1.10 (3H, 12-CH_3, s), 1.05 (3H, 4-CH_3, ov), 1.03 (3H, 10-CH_3, ov), 0.91 (8-CH_3, d), 0.89 (15-CH_3, t).

^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 177.35 (1-*C*O), 173.69 (4‴-*C*O), 171.42 (L_1-*C*O), 165.52 (12‴-*C*O), 147.51 (2‴-CH), 138.72 (6‴-C), 136.27 (9‴-C), 132.53 (7‴-CH), 128.70 (10‴-C), 126.60 (5‴-CH), 114.86 (8‴-CH), 110.28 (3‴-C), 101.78 (1′-CH), 94.15 (1″-CH), 84.39 (11-CH), 82.93 (5-CH), 78.35 (4″-CH), 77.41 (3-CH), 77.15 (13-CH), 73.79 (12-C), 72.54 (6-C), 72.54 (3″-C), 70.41 (2′-CH), 70.41 (9-CH_2), 67.20 (5′-CH), 64.90 (3′-CH), 62.14 (10-CH), 62.02 (5″-CH), 61.50 (11O-CH_3), 60.22 (13‴-CH_2), 57.02 (L_{10}-CH_2), 52.92 (L_3-CH_2), 52,45 (L_2-CH_2), 52.31 (L_7, L_8-CH_2), 48.79 (3″O*C*H_3), 48.17 (11‴-CH), 44.83 (2-CH), 42.14 (7-CH_2), 42.06 (4-CH), 39.74 (3′N-(*C*H_3)$_2$), 35.30 (9N-CH_3), 34.50 (2″-CH_2), 32.44 (L_{12}-C), 31.96 (L_5, L_6-CH_2), 29.06 (4′-CH_2), 27.78(L_{11}-C), 27.05 (6-CH_3), 26.13 (8-CH), 22.20 (8-CH_3), 21.58 (5′-CH_3), 21.15 (14-CH_2), 20.73 (3″-CH_3), 17.11 (12-CH_3), 16.44 (5″-CH_3), 14.01 (15‴-CH_2), 13.94 (14‴-CH_3), 13.81 (2-CH_3), 10.66 (15-CH_3), 8.62 (4-CH_3), 6.59 (10-CH_3).

4.18. 9-Deoxo-4“-*O*-(3-{4-[3-(1-cycloproyp-3-ethoxycyrbonyl-1,4-dihydro-4-oxo-quinolin-6-yl)propyl]piperazine-1-il}propyonyl)-9a,11-*O*-dimethyl-9a-aza-9a-homoerythromycin A (25)

Applying the same protocol as for the synthesis of compound **22**, compound **25** was obtained from **19** (0.11 g, 0.01 mmol) after filtration of the catalyst and evaporation of organic solvent product **25** (0.01 g, Y = 5%) as white crystalline product.

MS(*m/z*): calcd for MH^+: 1200.55, found. 1199.54 (48.20%).

^{1}H NMR (500 MHz, $CDCl_3$) δ**:** 8.54 (1H, 2‴-H, s), 8.53 (1H, 5‴-H, d), 7.73 (1H, 8‴-H, d), 7.71 (1H, 7‴-H, dd), 5.17 (1H, 1″-H, d), 4.69 (1H, 13-H, dd), 4.73 (1H, 4″-H, d), 4.59 (1H, 1′-H., d), 4.48 (1H, 5″-H, ov), 4.40 (2H, 13‴-CH_2, ov), 4.35 (1H, 3-H, ov), 3.80 (1H, 5′-H, m), 3.64 (1H, 5-H, d), 3.59 (3H, 11O-CH_3, s), 3.47 (2H, 11‴-CH, m), 3.40 (1H, 11-H, s), 3.33(3H, 3″O-CH_3, s), 3.28 (1H, 2′-H, dd), 2.77 (2H, L_{12}-CH_2, ov), 2.75 (1H, 2-H, ov), 2.70 (2H, L_3-CH_2, ov), 2.69 (1H, 10-H, ov), 2.69 (4H, L_7, L_8-CH_2, ov), 2.59 (1H, 3′-H, ov), 2.55 (2H, L_2-CH_2, ov), 2.54 (4H, L_5, L_6-CH_2, ov), 2.52(1H, 9a-H, ov), 2.40 (1H, 2″a-H, d), 2.32 (6H, 3′N-(CH_3)$_2$, s), 2.30 (2H, L_{10}-CH_2, s), 2.27 (3H, 9N-CH_3, s), 2.09 (1H, 9b-H, t), 2.00 (1H, 4-H, ov), 1.96 (1H, 8-H, ov), 1.92 (1H, 14a-H, m), 1.85 (2H, L_{11}-CH_2, ov), 1.72 (1H, 7a-H, d), 1.67 (1H, 4′a-H, m), 1.60 (1H, 2″b-H, dd), 1.35 (3H, 15‴-CH_2, dq), 1.48 (1H, 14b-H, m), 1.41 (3H, 14‴-CH_3, t), 1.31 (1H, 7b-H, ov), 1.26 (3H, 6-CH_3, s), 1.26 (1H, 4′b-H, ov), 1.22 (3H, 3″-CH_3, s), 1.20 (3H, 2-CH_3, d), 1.17 (3H, 5″-CH_3, d), 1.15 (3H, 5′-CH_3, d), 1.13 (3H, 12-CH_3, s), 1.13 (2H, 16‴-CH_2, dq), 1.06 (3H, 4-CH_3, d), 1.03 (3H, 10-CH_3, d), 0.91 (8-CH_3, d), 0.89 (15-CH_3, t).

^{13}C NMR (125 MHz, $CDCl_3$) δ**:** 177.60 (1-CO), 172.52 (4‴-CO), 171.90 (L_1-CO), 165.49 (12‴-CO), 147.49 (2‴-CH), 139.85 (9‴-C), 139.40 (6‴-C), 135.55 (7‴-CH), 130.99 (5‴-CH), 128.30 (10‴-C), 116.45 (8‴-CH), 111.30 (3‴-C), 102.00 (1′-CH), 94.70 (1″-CH), 83.20 (5-CH), 78.88 (4″-CH), 78.36 (3-CH), 77.70 (13-CH), 84.95 (11-CH), 73.00 (6-C), 74.74(12-C), 73.10 (3″-C), 70.92 (2′-CH), 70.90 (9-CH_2), 67.50 (5′-CH), 65.43 (3′-CH), 62.70 (5″-CH), 62.44 (10-CH), 62.07 (11O-CH_3), 60.90 (13‴-CH_2), 57.62 (L_{10}-CH_2), 53.30 (L_3-CH_2), 52.68 (L_2-CH_2), 52.00 (L_7, L_8-CH_2), 49.36 (3″O-CH_3), 45.30 (2-CH), 42.64 (4-CH), 42.00 (7-CH_2), 40.26 (3′N-(CH_3)$_2$), 35.80 (9N-CH_3), 35.01 (2″-CH_2), 32.42 (L_{12}-CH_2), 34.41 (11‴-CH), 32.40 (L_5, L_6-CH_2), 29.41 (4′-CH_2), 27.78(L_{11}-CH_2), 27.21 (6-CH_3), 26.64 (8-CH), 22.02 (8-CH_3), 21.85 (3″-CH_3), 21.66 (14-CH_2), 21.13 (5′-CH_3), 17,64 (5″-CH_3), 16.88 (12-CH_3), 14.38 (2-CH_3), 14.33 (14‴-CH_3), 11.20 (15-CH_3), 9.18 (4-CH_3), 8.13 (15‴-CH_2), 8.13 (16‴-CH_2), 7.09 (10-CH_3).

4.19. 9-Deoxo-4″-*O*-(3-{4-[3-(1-ethyl-3-carboxy-1,4-dihydro-4-oxo-quinolin-6-yl)propyl]piperazine-1-yl}propyonyl)-9a,11-*O*-dimethyl-9a-aza-9a-homoerythromycin A (26)

Applying the same protocol as for the synthesis of compound **22**, compound **26** was obtained from **20** (0.05 g, 0.04 mmol) after filtration of the catalyst and evaporation of organic solvent product **26** (0.05 g, Y = 90%) as yellow crystalline product.

MS(*m/z*): calcd for MH^+: 1160.49, found. 1161.53 (78.85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (1H, 2‴-H, s), 8.37 (1H, 5‴-H, d), 7.68 (1H, 7‴-H, dd), 7.56 (1H, 8‴-H, d), 5.16 (1H, 1″-H, dd), 4.69 (1H, 13-H, ov), 4.69 (1H, 4″-H, ov), 4.58 (1H, 1′-H, d), 4.39 (1H, 3-H, ov), 4.39 (1H, 5″-H, ov), 4.39 (2H, 11‴-CH_2, ov), 3.79 (1H, 5′-H, m), 3.61 (1H, 5-H, ov), 3.58 (3H, 11O-CH_3, s), 3.40 (1H, 11-H, s), 3.32 (1H, 2′-H, ov), 3.32 (3H, 3″O-CH_3, s), 2.83 (2H, L_{12}-CH_2, m), 2.74 (1H, 2-H, ov), 2.72 (2H, L_2-CH_2, ov), 2.68 (1H, 10-H, ov), 2.68 (1H, 3′-H, ov), 2.68 (8H, L_5, L_6, L_7, L_8-CH_2, ov), 2.52 (2H, L_3-CH_2, ov), 2.52 (1H, H-9a, ov), 2.41 (1H, 2″a-H), 2.36 (2H, L_{10}-CH_2, ov), 2.36 (6H, 3′N(CH_3)$_2$, s), 2.24 (3H, 9 N-CH_3, s), 2.07 (1H, 8-H, ov), 2.07 (1H, 9b-H, ov), 2.00 (1H, 4-H, ov), 1.89 (1H, 14a-H, ov), 1.89 (2H, L_{11}-CH_2, ov), 1.73 (1H, 7a-H, ov), 1.73 (1H, 4′a-H, ov), 1.60 (1H, 2″b-H, ov), 1.60 (3H, 15‴-CH_3, ov), 1.47 (1H, 14b-H, m), 1.28 (1H, 7b-H, ov), 1.28 (1H, 4′b-H, ov), 1.26 (3H, 6-CH_3, s), 1.20 (3H, 2-CH_3, ov), 1.20 (3H, 5′-CH_3, ov), 1.14 (3H, 5″-CH_3, ov), 1.13 (3H, 3″-CH_3, ov), 1.11 (3H, 12-CH_3, ov), 1.04 (3H, 4-CH_3, ov), 1.04 (3H, 10-CH_3, ov), 0.91 (3H, 8-CH_3, ov), 0.90 (3H, 15-CH_3, ov).

^{13}C NMR (300 MHz, $CDCl_3$) δ 178.39 (1-*C*O), 177.95(4‴-*C*O), 172.04 (L1-*C*O), 167.29 (12‴-*C*O), 147.44 (2‴-CH), 140.81 (6‴-C), 137.49 (9‴-C), 134.85 (7‴-CH), 126.66 (10‴-C), 126.35 (5‴-CH), 116.31 (8‴-CH), 108.83 (3‴-C), 102.23(1′-CH), 94.82 (1″-CH), 85.06 (11-H), 83.67 (5-CH), 78.97 (4″-CH), 78.10 (3-H), 77.88 (13-CH), 74.43 (12-CH), 73.22 (3″-C), 73.17 (6-C), 71.08 (2′-CH), 70.11 (9-CH_2), 67.51 (5′-CH), 65.51 (3′-CH), 62.83 (5″-CH), 62.70 (10-H), 62.15 (11O-CH_3), 57.45 (L_{10}-CH_2), 53.48 (L_2-CH_2), 53.02 (L_7, L8-CH_2), 52.81 (L_5, L_6-CH_2), 49.70 (11‴-CH_2), 49.45 (3″O-$_{CH3}$), 45.47 (2-CH), 42.77 (7-CH_2), 42,62 (4-CH), 40.45 (3′N-CH_3), 35.93 (9 N-$_{CH3}$), 35.14 (2″-CH_2), 33.01 (L_{12}-CH_2), 32.54 (L_3-CH_2), 29.70 (4′-CH_2), 28.18 (L_{11}-CH_2), 27.67 (6-CH_3), 26.75 (8-CH), 22.23 (8-CH_3), 21.78 (14-CH_2), 21.75 (5′-CH_3), 21.36 (3″-CH_3), 17.75 (5″-CH_3), 17.12 (12-CH_3), 14.74 (15‴-CH_3), 14.67 (2-CH_3), 11.29 (15-CH_3), 9.37 (4-CH_3), 7.22 (10-CH_3).

4.20. 9-Deoxo-4″-*O*-(3-{4-[3-(1-ethyl-3-etoksikathoxycarbonylrbonil-1,4-dihydro-4-oxo-quinolin-6-ill)propropylpil]piperazine-1-yl}propyonyl)-9a-methyl-9a-aza-9a-homoerythromycin A (27)

Applying the same protocol as for the synthesis of compound **22**, compound **27** was obtained from **21** (0.25 g, 0.21 mmol) after filtration of the catalyst and evaporation of organic solvent product was purified by low-pressure column chromatography in system of solvents and DCM/MeOH/NH_3 = 90:5:0.5; after warded **27** (0.03 g, Y = 13%) as white crystalline product.

MS(*m/z*): calcd for MH^+: 1174.51, found: 1175.04 (70.26%).

HRMS calcd for $C_{62}H_{104}N_5O_{16}$ $(M+H)^+$ 1174.7478; found 1174.7542.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.68 (1H, 2‴-H, s), 8.05 (1H, 5‴-H, d), 7.74 (1H, 8‴-H, d), 7.64 (1H, 7‴-H, dd), 4.92 (1H, 1″-H, dd), 4.75 (1H, 13-H, ov), 4.55 (1H, 4″-H, ov), 4.47 (1H, 1′-H, d), 4.41 (2H, 11‴-CH, q), 4.34 (1H, 5″-H, ov), 4.23 (2H, 13‴-CH_2, ov), 4.17 (1H, 3-H, ov), 3.73 (1H, 5′-H, m), 3.48 (1H, 5-H, d), 3.45 (1H, 11-H, s), 3.22 (3H, 3″O-CH_3, s), 3.05 (1H, 2′-H, dd), 2.73 (2H, L_{12}-CH_2, ov), 2.71 (1H, 10-H, ov), 2.67 (1H, 2-H, ov), 2.57 (2H, L_3-CH_2, ov), 2.45 (4H, L_5, L_6-CH_2, ov), 2.43 (2H, L_2-CH_2, ov), 2.40 (1H, 3′-H, ov), 2.39 (1H, 9a-H, ov), 2.37 (1H, 2′-CH), 2.35 (L_{10}-CH_2, ov), 2.34 (1H, 2″a-H, d), 2.21 (6H, 3′N-(CH_3)$_2$, ov), 2.21 (3H, 9N-CH_3, ov), 2.12 (1H,

9b-H, t), 1.91 (1H, 4-H, ov), 1.88 (L_{11}-CH_2, ov), 1.77 (1H, 14a-H, m), 1.68 (1H, 2″b-H, dd), 1.58 (1H, 4′a-H, m), 1.50 (1H, 7a-H, d), 1.36 (3H, 15‴-CH_2, t), 1.29 (3H, 14‴-CH_3, t), 1.27 (1H, 7b-H, ov), 1.16 (1H, 14b-H, ov), 1.16 (3H, 6-CH_3, ov), 1.15 (1H, 4′b-H, ov), 1.10 (3H, 5′-CH_3, ov), 1.09 (3H, 3″-CH_3, ov), 1.08 (3H, 2-CH_3, ov), 1.04 (3H, 5″-CH_3, ov), 1.02 (3H, 12-CH_3, ov), 0.96 (3H, 4-CH_3, ov), 0.95 (3H, 10-CH_3, ov), 0.86 (8-CH_3, d), 0.80 (15-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:** 177.61 (1-CO), 173.24 (4‴-CO), 172.11 (L_1-CO), 165.24 (12‴-CO), 148.98 (2‴-CH), 139.37 (6‴-C), 137.31 (9‴-C), 133.76 (7‴-CH), 129.03 (10‴-C), 125.90 (5‴-CH), 117.62 (8‴-CH), 110.30 (3‴-C), 102.61 (1′-CH), 94.91 (1″-CH), 83.91 (5-CH), 78.45 (4″-CH), 77.97 (3-CH), 76.89 (13-CH), 75.46 (11-CH), 74.11 (3″-C), 73.18 (12-CH), 72.99 (6-C), 71.03 (2′-CH), 69.18 (9-CH_2), 67.28 (5′-CH), 65.40 (3′-CH), 62.73 (5″-CH), 62.00 (10-CH), 57.04 (L_{10}-CH_2), 53.13 (L_2, L_3-CH_2), 49.33 (3″O-CH_3), 48.72 (11‴-CH_2), 45.13 (2-CH), 42.28 (7-CH_2), 42.20 (4-CH), 40.86 (3′N-$(CH_3)_2$, 36.29 (9N-CH_3), 34.84 (2″-CH_2), 32.99 (L_5, L_6-CH_2), 32.73 (L_{12}-CH_2), 30.69 (4′-CH_2), 28.47 (14-CH_2) ,27.98 (6-CH_3), 27.76 (L_{11}-CH_2), 25.93 (8-CH_3), 22.61 (8-CH_3), 22.32 (5′-CH_3), 21.48 (14-CH_2), 21.24 (3″-CH_3), 18.29 (12-CH_3), 18.22 (5″-CH_3), 15.16 (2-CH_3), 14,95 (15‴-CH_3), 14.85 (14‴-CH_3), 11.48 (15-CH_3), 9.51 (2-CH_3), 7.30 (10-CH_3).

IR (KBr, cm^{-1}) 2953, 2922, 2852, 1690, 1613, 1453, 1378, 1318, 1238, 1169, 1079, 1013, 893, 863, 811.

4.21. Ethyl 1-ethyl-6-(3-hydroxy-1-propyn-1-yl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate (29)

Applying the same protocol as for the synthesis of compound **7**, compound **29** was obtained from ethyl 1-ethyl-6-iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylate **4** (2.60 g, 7.00 mmol) and propargyl alcohol **28** (0.50 mL, 8.4 mmol) as crude crystalline product **29** (2.03 g, Y = 97%) as white crystalline product.

MS(*m/z*): calcd for MH^+: 299.58, found: 300.2 (83.9%).

HRMS calcd for $C_{17}H_{18}NO_4$ $(M+H)^+$ 300.1230; found 300.1106.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.70 (1H, 2‴-H, s), 8.22 (1H, 5‴-H, d), 7.82 (1H, 8‴-H, d), 7.77 (1H, 7‴-H, dd), 4.42 (2H, 11‴-CH_2, q), 4.35 (2H, L_{10}-CH_2, s), 4.23 (2H, 13‴-CH_2, q), 1.37 (3H, 15‴-CH_3, t), 1.30 (3H, 14‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:**172.03 (4‴-CO), 164.46 (12‴-CO), 149.20 (2‴-CH), 138.22 (9‴-C), 134.83 (7‴-CH), 129.07 (10‴-C), 128.77 (5‴-CH), 118.75 (6‴-C), 117.97 (8‴-CH), 110.56 (3‴-C), 90.86 (L_{11}-CH), 82.59 (L_{12}-CH), 59.81 (13‴-CH_2), 49.45 (L_{10}-CH_2), 48.00 (11‴-CH_2), 14.30 (15‴-CH_3), 14.30 (14‴-CH_3).

4.22. Ethyl 1-ethyl-6-[(1*Z*)-3-hydroxy-1-propen-1-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylate (30)

To the solution of **29** (0.5 g, 1.67 mmol) in DMC (4 mL) and ethanol (4 mL) Lindlar catalyst (0.18 g. Pd/$CaCO_3$-Pb 5%) was added. Reaction mixture was hydrogenated (p = atm t = 25 °C) for 4 h. Catalyst was filtered off and solvent evaporated yielding title product **30** (0.47 g, Y = 93%).

MS(*m/z*): calcd for MH^+: 302.34, found: 302.1 (95.5%).

HRMS calcd for $C_{17}H_{20}NO_4$ $(M+H)^+$ 300.1230; found 300.1206.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.69 (1H, 2‴-H, s), 8.06 (1H, 5‴-H, d), 7.67 (1H, 7‴-H, dd), 7.82 (1H, 8‴-H, d), 6.54 (1H, L_{12}-CH, d), 5.91 (1H, L_{11}-CH, dt), 4.42 (2H, 11‴-CH_2, q), 4.24 (2H, 13‴-CH_2, q), 4.30 (2H, L_{10}-CH_2, ddd), 1.38 (3H, 15‴-CH_3, t), 1.31 (3H, 14‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:**173.08 (4‴-CO), 165.04 (12‴-CO), 149.11 (2‴-CH), 137.78 (9‴-C), 133.49 (6‴-C), 127.65 (L_{12}-CH), 133.53 (7‴-CH), 135.29 (L_{11}-CH), 128.56 (10‴-C), 126.38 (5‴-CH), 117.63 (8‴-CH), 110.59 (3‴-C), 60.09 (L_{10}-CH_2), 60.32 (13‴-CH_2), 48.32 (11‴-CH_2), 14.78 (15‴-CH_3), 14.71 (14‴-CH_3).

4.23. Ethyl 6-[(1*E*)-3-({[(1,1-dimethylethyl)oxy]carbonyl}oxy)-1-propen-1-yl]-1-ethyl-4-oxo-1,4-dihydro-3-quinolinecarboxylate (32)

To the solution of 30 (0.29 g, 0.96 mmol) in DCM (5 mL) at 0 °C bis(1,1-dimethylethyl) dicarbonate **31** (0.377 g, 1.73 mmol), and tetrabutylamoniumhydrogen sulfate (0.0195 g, 0.06 mmol) were added. Than to the reaction mixture was dropped solution of NaoH (0.115 g, 2.88 mmol) in water (0.35 mL). Reaction mixture was stirred gradually to 25 °C and stirred over night. To the reaction mixture were added DCM (20 mL) and water (20 mL). Layers were separated, water layer was extracted with DCM (2 × 10 mL) and collected organic extracts were dried (K_2CO_3) and concentrated under vacuum and residue was dissolved in EtOAc. *n*-hexane 1/10 and precipitate was filtered off to afford pure product **33** (0.354 g, Y = 92%).

MS(*m/z*): calcd for MH^+: 402.46, found: 402.2 (90.58%).

HRMS calcd for $C_{22}H_{27}NO_6$ $(M+H)^+$ 300.1230; found 300.1206.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.70 (1H, 2‴-H, s), 8.09 (1H, 5‴-H, d), 7.85 (1H, 8‴-H, d), 7.69 (1H, 7‴-H, dd), 6.80 (1H, L_{12}-CH, d), 5.89 (1H, L_{11}-CH, dt), 4.85 (2H, L_{10}-CH_2, dd), 4.42 (2H, 11‴-CH_2, q), 4.24 (2H, 13‴-CH_2, q), 1.42 (9H, L_1-CH_3, s), 1.37 (3H, 15‴-CH_3, t), 1.30 (3H, 14‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:**172.51 (4‴-CO), 164.53 (12‴-CO), 152.69 (L_3-CO), 148.84 (2‴-CH), 137.72 (9‴-C), 132.90 (7‴-CH), 132.04 (6‴-C), 130.94 (L_{12}-CH), 128.10 (10‴-C), 126.91 (L_{11}-CH), 126.07 (5‴-CH), 117.46 (8‴-CH), 110.22 (3‴-C), 81.65 (L_2-C), 63.11 (L_{10}-CH_2), 59.65 (13‴-CH_2), 47.86 (11‴-CH_2), 27.24 (L_1-CH_3), 14.32 (14‴-CH_3), 14.23 (15‴-CH_3).

4.24. Ethyl 6-[(1*E*)-3-(4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-piperazinyl)-1-propen-1-yl]-1-ethyl-4-oxo-1,4-dihydro-3-quinolinecarboxylate (34)

To the dry solution of **33** (0.085 g, 0.45 mmol) in toluene (5 mL) were added **32** (0.2 g, 0.5 mmol), $Pd_2(dba)_3$ (0.123 g, 0.135 mmol) and dppb (0.115 g, 0.27 mmol). Reaction mixture was refluxed for 3 h. Solvent was evaporated and to the residue EtOAc was added, catalyst precipitated, and filtered off. Solvent was evaporated and residue was dissolved in DCM, n-hexane was added and precipitate was filtered off. Precipitate was dissolved in MeCN but crystal was not obtained and solvent was evaporated yielding brown oily product (0.2279 g, Y = 99%).

MS(*m/z*): calcd for MH^+: 470.58, found: 470.4 (68.45%), LC-UV (91.7%).

HRMS calcd for $C_{26}H_{36}N_3O_5$ $(M+H)^+$ 470.2649; found 470.2646.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.66 (1H, 2‴-H, s), 8.17 (1H, 5‴-H, d), 7.95 (1H, 7‴-H, dd), 7.77 (1H, 8‴-H, d), 6.71 (1H, L_{12}-CH, d), 6.42 (1H, L_{11}-CH, dt), 4.41 (2H, 11‴-CH_2, q), 4.24 (2H, 13‴-CH_2, q), 3.33 (4H, L_5, L_6-CH_2, ov), 3.15 (2H, L_{10}-CH_2, d), 2.37 (4H, L_7, L_8-CH_2, m), 1.39 (9H, L_1-CH_3, s), 1.37 (3H, 15‴-CH_3, t), 1.30 (3H, 14‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:**173.22 (4‴-CO), 165.16 (12‴-CO), 154.41 (L_3-CO), 149.08 (2‴-CH), 138.29 (9‴-C), 133.82 (6‴-C), 131.04 (L_{12}-CH), 130.58 (7‴-CH), 129.51 (L_{11}-CH), 129.07 (10‴-C), 124.56 (5‴-CH), 118.16 (8‴-CH), 110.75 (3‴-C), 79.26 (L_2-C), 60.49 (L_{10}-CH_2), 60.22 (13‴-CH_2), 52.95 (L_7, L_8-CH_2), 48.48 (11‴-CH_2), 40.94 (L_5, L_6-CH_2), 28.61 (L_1-CH_3), 14.96 (15‴-CH_3), 14.87 (14‴-CH_3).

IR (KBr, cm^{-1}) 3433, 2973, 2939, 1737, 1459, 1376, 1346, 1315, 1273, 1169, 1113, 1080, 1056, 1015, 1000, 959, 905.

4.25. Ethyl 1-ethyl-4-oxo-6-[(1*E*)-3-(1-piperazinyl)-1-propen-1-yl]-1,4-dihydro-3-quinolinecarboxylate (35)

To the solution of **34** (0.185 g, 0.394 mmol) in DCM (1.85 mL) was added CF_3COOH (1.85 mL, 0.024 mol). Reaction mixture was

stirred at rt for 2.5 h. To the reaction mixture were added DCM (20 mL) and water (20 mL). Layers were separated, water layer was extracted with DCM (2 × 10 mL) and to the water layer DCM (20 mL) was added and pH adjusted from 1.8 to 9.5 by addition of aq soln NH_4OH. Layers were separated; water layer was extracted with DCM (2 × 15 mL). The organic extract was dried (K_2CO_3) and concentrated under vacuum to afford title product **35** (0.689 g, Y = 47.6%).

MS(*m/z*): calcd for MH^+: 370.46, found: 369.6 (68.45%), LC-UV (91.7%).

HRMS calcd for $C_{21}H_{28}N_3O_3$ $(M+H)^+$ 370.2125; found 370.2114.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.66 (1H, 2‴-H. s), 8.17 (1H, 5‴-H, d), 7.76 (1H, 8‴-H, d), 7.95 (1H, 7‴-H, dd), 6.70 (1H, L_{12}-CH, d), 6.40 (1H, L_{11}-CH, dt), 4.41 (1H, 11‴-CH, q), 4.24 (2H, 13‴-CH_2, q), 3.11 (2H, L_{10}-CH_2, d), 2.77 (4H, L_5, L_6-CH_2, ov), 2.39 (4H, L_7, L_8-CH_2, ov), 1.37 (2H, 15‴-CH_2, dd), 1.29 (3H, 14‴-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:** 172.61 (4‴-CO), 164.53 (12‴-CO), 148.49 (2‴-CH), 137.68 (9‴-C), 133.25 (6‴-C), 130.73 (L_{12}-CH), 129.94 (7‴-CH), 128.41 (10‴-C), 128.41 (L_{11}-CH), 123.86 (5‴-CH), 117.56 (8‴-CH), 110.05 (3‴-C), 60.53 (L_{10}-CH_2), 59.61 (13‴-CH_2), 53.24 (L_7, L_8-CH_2), 47.86 (11‴-CH), 45.08(L_5, L_6-CH_2), 14.35 (15‴-CH_3), 14.25 (14‴-CH_3).

IR (KBr, cm^{-1}) 3417, 3292, 2942, 2850, 1725, 1625, 1609, 1588, 1496, 1496, 1453, 1385, 1453, 1385, 1335, 1307, 1224, 1184, 1161, 1125, 1087, 1031, 995, 937.

4.26. 2′-*O*-Acetyl-11-*O*,12-*O*-carbonyl-4"-*O*-{3-[4-((2*E*)-3-{1-ethyl-3-[(ethyloxy)carbonyl]-4-oxo-1,4-dihydro-6-quinolinyl}-2-propen-1-yl)-1-piperazinyl]propyl}-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (38)

To the solution of **36** (0.355 g. 0.41 mmol) in DCM (5 mL) was added Dess–Martin periodinane (0.209 g. 0.49 mmol). Reaction mixture was stirred at rt for 3 h. According to TLC performed in DCM/MeOH/NH_4OH = 90/9/0.5 conversion was complete. Precipitate was filtered off and to the residue **35** (0.3 g. 0.81 mmol). NaB-H(AOc)$_3$ (0.172 g. 0.81 mmol) and $ZnCl_2$ (0.056 g. 0.41 mmol) were added. Reaction mixture was stirred at rt over night. Solvent was evaporated and residue (1.0863 g) was purified by flash chromatography on a 20 g silica gel column. Product was eluted with a system of solvents EtOAc/*n*-hexane/TEA 100/100/20, after warded **38** (0.14 g, Y = 28%) as white crystalline product.

MS(*m/z*): calcd for MH^+: 1227.55, found: 1226.7 (73.44%).

HRMS calcd for $C_{65}H_{104}N_5O_{17}$ $(M+H)^+$ 1226.7422; found 1226.7442.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.47 (1H, 2‴-H, ov), 8.47 (1H, 5‴-H, ov), 7.75 (1H, 7‴-H, dd), 7.45 (1H, 8‴-H, d), 6.65 (2H, L_{12}-CH, d), 6.40 (1H, L_{11}-CH, dt), 5.06 (1H, 1″-H, dd), 4.89 (1H, 13-H, ov), 4.75 (1H, 2′-H, dd), 4.55 (1H, 1′-H, d), 4.25 (2H, 11‴-CH, q), 4.25 (1H, 5″-H, ov), 4.43 (1H, 11-H, s), 4.42 (1H, 3-H, ov), 4.40 (2H, 13‴-CH_2, ov), 3.67 (2H, L_1-CH_2, ov), 3.65 (1H, 5′-H, m), 3.54 (1H, 5-H, d), 3.33 (3H, 3″O-CH_3, s), 3.22 (L_{10}-CH_2, d), 2.85 (1H, 2-H, ov), 2.84 (1H, 10-H, ov), 2.78 (1H, 4″-H, ov), 2.75 (1H, 3′-H, ov), 2.58 (8H, L_5, L_6, L_7, L_8-CH_2, ov), 2.44 (2H, L_3-CH_2, ov), 2.39 (1H, 9a-H, ov), 2.30 (1H, 2″a-H, d), 2.26 (6H, 3′N-$(CH_3)_2$, ov), 2.21 (3H, 9N-CH_3, ov), 2.07 (1H, 9b-H, t), 2.07 (3H, 2′-CH_3, s), 1.94 (1H, 8-CH, ov), 1.84 (1H, 4-H, ov), 1.81 (2H, L_2-CH_2, ov), 1.79 (1H, 14a-H, m), 1.70 (1H, 4′a-H, m), 1.58 (1H, 7a-H, d), 1.55 (3H, 15‴-CH_2, t), 1.51 (1H, 2″b-H, dd), 1.51 (1H, 14b-H, ov), 1.42 (3H, 14‴-CH_3, t), 1.41 (3H, 12-CH_3, ov), 1.33 (1H, 7b-H, ov), 1.30 (3H, 5″-CH_3, ov), 1.27 (3H, 6-CH_3, ov), 1.27 (1H, 4′b-H, ov), 1.26 (3H, 3″-CH_3, ov), 1.21 (3H, 5′-CH_3, ov), 1.19 (3H, 2-CH_3, ov), 1.05 (3H, 10-CH_3, ov), 0.94 (3H, 4-CH_3, ov), 0.92 (8-CH_3, d), 0.88 (15-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:**177.57 (1-CO), 174.52 (4‴-CO), 170.28 (2′-CO), 166.24 (12‴-CO), 153.73 (11,12-CO), 148.49 (2‴-CH), 138.15 (9‴-C), 134.23 (6‴-C), 132.13 (L_{12}-CH_2), 130.33 (7‴-CH), 129.78 (10‴-C), 128.25 (L_{11}-CH_2), 126.26 (5‴-CH), 116.18 (8‴-CH), 111.55 (3‴-C), 100.29 (1′-CH), 95.48 (1″-CH), 88.19 (4″-CH), 86.56 (11-CH), 85.19 (12-CH), 83.79 (5-CH), 77.62 (3-CH), 76.45 (13-CH), 74.25 (3″-C), 73.82 (6-C), 72.19 (L_1-CH_2), 70.89 (2′-CH), 68.19 (5′-CH), 68.09 (9-CH_2), 64.89 (5″-CH), 63.54 (3′-CH), 61.61 (10-CH), 61.20 (13‴-CH_2), 60.96 (L_{10}-CH_2), 55.44 (L_3-CH_2), 53.03 (L_5-L_8-CH_2), 49.89 (3″O-CH_3), 49.18 (11‴-CH_2), 45.21 (2-CH), 43.93 (7-CH_2), 41.69 (4-CH), 41.00 (3′N-$(CH_3)_2$), 36.09 (2″-CH_2), 34.76 (9N-CH_3), 31.09 (4′-CH_2), 27.87 (L_2-CH_2), 27.17 (6-CH_3), 26.57 (8-CH_3), 22.42 (14-CH_2), 22.36 (3″-CH_3), 21.99 (8-CH_3), 21.87 (2′-CH_3), 21.76 (5′-CH_3), 18.80 (5″-CH_3), 15.17 (2-CH_3), 14.87 (15‴-CH_3), 14.75 (14‴-CH_3), 14.18 (12-CH_3), 11.66 (4-CH_3), 10.70 (15-CH_3), 5.55 (10-CH_3).

IR (KBr, cm^{-1}) 3437, 1969, 2825, 1728, 1634, 1609, 1552, 1478, 1456, 1380, 1276, 1257, 1170, 1110, 1092, 1046, 1013, 982, 959, 899.

4.27. 4"-*O*-[(3-{4-[(2*E*)-3-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-6-quinolinyl)-2-propen-1-yl]-1-piperazinyl}propyl)-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (39)

To the solution of **13** (0.1145 g. 0.093 mmol) in MeOH (7.5 mL) was added solution of K_2CO_3 (0.232 g. 1.68 mmol) in water (2.5 mL) and heated to 50 °C for 5 h. Reaction mixture was stirred at rt over night. MeOH was evaporated and to the residue DCM (20 mL) and water (15 mL) were added. Layers were separated and water layer extracted with DCM (2 × 20 mL). The organic extract was dried (K_2CO_3) and concentrated under vacuum to afford title product **13** (0.0982 g. yield 93.3%). Product was dissolved in EtOAc. *N*-Hexane was added and precipitate was filtered off to afford pure product (0.0693 g. yield 65.7%).

MS(*m/z*): calcd for MH^+: 1130.46, found: 1130.8 (94.63%). LC-UV (97.15%).

HRMS calcd for $C_{60}H_{100}N_5O_{15}$ $(M+H)^+$ 1130.7210; found 1130.7212.

^{1}H NMR (500 MHz, DMSO) δ**:** 8.74 (1H, 2‴-H, s), 8.47 (1H, 5‴-H, d), 7.87 (1H, 7‴-H, dd), 7.58 (1H, 8‴-H, d), 6.67 (2H, L_{12}-CH, d), 6.47 (1H, L_{11}-CH, dt), 5.12 (1H, 1″-H, dd), 4.72 (1H, 13-H, ov), 4.52 (1H, 1′-H, d), 4.37 (2H, 11‴-CH, q), 4.29 (1H, 5″-H, ov), 4.24 (1H, 3-H, ov), 3.65 (1H, 11-H, s), 3.64 (2H, L_1-CH_2, ov), 3.75 (1H, 5′-H, m), 3.61 (1H, 5-H, d), 3.32 (3H, 3″O-CH_3, s), 3.22 (L_{10}-CH_2, ov), 3.19 (1H, 2′-H, ov), 2.77 (1H, 4″-H, ov), 2.74 (1H, 2-H, ov), 2.67 (1H, 10-H, ov), 2.52 (1H, 9a-H, ov), 2.52 (1H, 3′-H, ov), 2.52 (8H, L_5, L_6, L_7, L_8-CH_2, ov), 2.44 (2H, L_3-CH_2, ov), 2.37 (1H, 2″a-H, d), 2.27 (6H, 3′N-$(CH_3)_2$, ov), 2.31 (3H, 9N-CH_3, ov), 2.03 (1H, 9b-H, t), 2.00 (1H, 8-CH, ov), 1.95 (1H, 4-H, ov), 1.89 (1H, 14a-H, m), 1.80 (1H, 7a-H, d), 1.77 (2H, L_2-CH_2, ov), 1.64 (1H, 4′a-H, m), 1.59 (3H, 15‴-CH_2, t), 1.50 (1H, 2″b-H, dd), 1.43 (1H, 14b-H, ov), 1.32 (3H, 6-CH_3, ov), 1.31 (3H, 5″-CH_3, ov), 1.27 (1H, 7b-H, ov), 1.24 (3H, 5′-CH_3, ov), 1.19 (1H, 4′b-H, ov), 1.19 (3H, 3″-CH_3, ov), 1.17 (3H, 2-CH_3, ov), 1.09 (3H, 10-CH_3, ov), 1.09 (3H, 12-CH_3, ov), 1.04 (3H, 4-CH_3, ov), 0.90 (8-CH_3, d), 0.88 (15-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ**:** 178.28 (1-CO), 178.00 (4‴-CO), 167.20 (12‴-CO), 147.50 (2‴-CH), 138.18 (9‴-C), 131.04 (L_{12}-CH_2), 131.50 (7‴-CH), 129.30 (L_{11}-CH_2), 125.00 (5‴-CH), 116.53 (8‴-CH), 102.45 (1′-CH), 94.88 (1″-CH), 87.81 (4″-CH), 73.92 (11-CH), 74.31 (12-CH), 83.14 (5-CH), 77.86 (3-CH), 77.53 (13-CH), 73.83 (3″-C), 73.71 (6-C), 72.72 (L_1-CH_2), 71.05 (2′-CH), 67.98 (5′-CH), 70.12 (9-CH_2), 64.81 (5″-CH), 65.36 (3′-CH), 62.40 (10-CH), 61.00 (L_{10}-CH_2), 52.00 (L_3-CH_2), 53.15 (L_5-L_8-CH_2), 49.62 (3″O-CH_3), 49.62 (11‴-CH_2), 45.26 (2-CH), 42.32 (7-CH_2), 42.07 (4-CH), 40.34 (3′N-$(CH_3)_2$), 35.49 (2″-CH_2), 36.31 (9N-CH_3), 28.77 (4′-CH_2), 27.57 (L_2-CH_2), 27.57 (6-CH_3), 26.80 (8-CH_3), 21.26 (14-CH_2), 21.88 (3″-CH_3), 21.98 (8-CH_3), 21.67 (5′-CH_3), 18.47 (5″-CH_3), 14.71 (2-CH_3), 14.72 (15‴-CH_3), 16.27 (12-CH_3), 9.11 (4-CH_3), 11.24 (15-CH_3), 7.42 (10-CH_3).

IR (KBr, cm^{-1}) 2978, 2933, 2799, 1718, 1695, 1625, 1608, 1585, 1550, 1495, 1455, 1419, 1392, 1365, 1342 1310, 1288, 1248, 1226, 1172, 1135, 1085, 1029, 995 937.

4.28. 4”-*O*-[(3-{4-[3-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-6-quinolinyl)propyl]-1-piperazinyl}propyl)-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (40)

Compound **14** (0.05 g. 0.04 mmol) was dissolved in MeOH (20 mL) and catalyst (0.01 g. Pd/C 10%) was added. Reaction mixture was hydrogenated (p = 2.2 bar. t = 25 °C) over night. Catalyst was filtered off and solvent evaporated yielding title product **15** (0.045 g. yield 90.0%). Product was dissolved in EtOAc. *n*-Hexane was added and precipitate was filtered off to afford pure product (0.0386 g. yield 78.0%).

MS(m/z): calcd for MH^+: 1132.48, found: 1132.7 (97.12%).

HRMS calcd for $C_{60}H_{102}N_5O_{15}$ $(M+H)^+$ 1132.7367; found 1132.7377.

^{1}H NMR (500 MHz, DMSO) δ: 8.78 (1H, 2‴-H, s), 8.36 (1H, 5‴-H, d), 7.69 (1H, 7‴-H, dd), 7.56 (1H, 8‴-H, d), 5.09 (1H, 1″-H, dd), 4.72 (1H, 13-H, ov), 4.55 (1H, 1′-H, d), 4.40 (2H, 11‴-CH, q), 4.25 (1H, 5″-H, ov), 4.19 (1H, 3-H, ov), 3.73 (1H, 5′-H, m), 3.71 (1H, 11-H, s), 3.63 (2H, L_1-CH_2, ov), 3.61 (1H, 5-H, d), 3.32 (3H, 3″O-CH_3, s), 3.30 (1H, 2′-H, ov), 2.83 (2H, L_{12}-CH, ov), 2.83 (1H, 3′-H, ov), 2.77 (1H, 4″-H, ov), 2.74 (1H, 2-H, ov), 2.72 (1H, 10-H, ov), 2.60 (8H, L_5, L_6, L_7, L_8-CH_2, ov), 2.56 (1H, 9a-H, ov), 2.50 (2H, L_3-CH_2, ov), 2.46 (6H, 3′N-$(CH_3)_2$, ov), 2.46 (L_{10}-CH_2, ov), 2.35 (3H, 9N-CH_3, ov), 2.33 (1H, 2″a-H, d), 2.11 (1H, 9b-H, t), 2.00 (1H, 8-CH, ov), 1.96 (1H, 4-H, ov), 1.92 (1H, L_{11}-CH, ov), 1.87 (1H, 14a-H, m), 1.81 (2H, L_2-CH_2, ov), 1.76 (1H, 4′a-H, m), 1.73 (1H, 7a-H, d), 1.60 (3H, 15‴-CH_2, t), 1.52 (1H, 2″b-H, dd), 1.45 (1H, 14b-H, ov), 1.32 (3H, 6-CH_3, ov), 1.31 (1H, 7b-H, ov), 1.30 (3H, 5″-CH_3, ov), 1.25 (1H, 4′b-H, ov), 1.23 (3H, 3″-CH_3, ov), 1.20 (3H, 5′-CH_3, ov), 1.17 (3H, 2-CH_3, ov), 1.12 (3H, 10-CH_3, ov), 1.10 (3H, 12-CH_3, ov), 1.03 (3H, 4-CH_3, ov), 0.92 (8-CH_3, d), 0.89 (15-CH_3, t).

^{13}C NMR (125 MHz, DMSO) δ:178.68 (1-CO), 178.39 (4‴-CO), 167.28 (12‴-CO), 147.54 (2‴-CH), 140.54 (6‴-C), 137.57 (9‴-C), 134.79 (7‴-CH), 126.73 (10‴-C), 126.38 (5‴-CH), 116.37 (8‴-CH), 108.90 (3‴-C), 102.06 (1′-CH), 94.89 (1″-CH), 87.99 (4″-CH), 83.20 (5-CH), 77.92 (3-CH), 77.34 (13-CH), 74.37 (12-CH), 73.91 (3″-C), 73.90 (6-C), 73.64 (11-CH), 72.62 (L_1-CH_2), 70.94 (2′-CH), 70.00 (9-CH_2), 67.40 (5′-CH), 65.38 (3′-CH), 64.75 (5″-CH), 62.82 (10-CH), 57.14 (L_{10}-CH_2), 54.92 (L_3-CH_2), 52.27 (L_5-L_8-CH_2), 49.68 (11‴-CH_2), 49.61 (3″O-CH_3), 45.29 (2-CH), 42.20 (7-CH_2), 42.20 (4-CH), 40.00 (3′N-$(CH_3)_2$), 36.37 (9N-CH_3), 35.45 (2″-CH_2), 32.99 (L_{12}-CH_2), 29.96 (4′-CH_2), 27.63 (L_{11}-CH_2), 27.24 (6-CH_3), 27.16 (L_2-CH_2), 26.72 (8-CH_3), 21.99 (8-CH_3), 21.73 (5′-CH_3), 21.73 (3″-CH_3), 21.35 (14-CH_2), 18.44 (5″-CH_3), 16.35 (12-CH_3), 14.73 (15‴-CH_3), 14.72 (2-CH_3), 11.22 (15-CH_3), 8.38 (4-CH_3), 7.52 (10-CH_3).

IR (KBr, cm^{-1}) 3412, 2970, 2937, 1724, 1614, 1576, 1476, 1403, 1383, 1274, 1170, 1109, 1084, 1060, 1014, 959.

4.29. In vitro antibacterial activity

Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method according to guidelines of the Clinical Laboratory Standards Institute,[34] except that for *Streptococcus* medium, lysed blood was substituted with 5% horse serum. Double dilutions of tested compounds were prepared using TECAN Genesis 150.[37] 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.

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