Supporting Information

Discovery of 4“-Ether Linked Azithromycin-Quinolone Hybrid Series: Influence of the Central Linker on the Antibacterial Activity

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Experimental Section

General Experimental Methods

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

inert atmosphere of dry argon. The course of the reaction was followed by chromatography on a thin layer (TLC) of silica gel (Merck 60 F_{254}) in solvent systems methylene chloride-methanol-ammonium hydroxide 25% (90:9:1.5, system A), (90:9:0.5), system A1) or methylene chloride-acetone (8:2, system B) (7:3, System C) unless otherwise stated. The separation of the reaction products and the purification of the products for the purpose of spectral analyses were performed on a silica gel column (Merck 60, 230-400 mesh, or 60-230 mesh in solvent systems A, B or C unless otherwise stated. Purity of tested compounds was determined by elemental analysis, and all compounds were at least 95% pure if not stated otherwise.

The structure of all novel compounds was confirmed by HRMS, and/or NMR spectroscopic methods. Complete and unambiguous assignments for all ^{1}H and ^{13}C resonances could be achieved on the basis of chemical shift considerations, coupling information (APT and gated decoupled ^{13}C NMR spectra), and COSY, HSQC, and HMBC spectra.

Determination of Minimum Inhibitory Concentration (MICs)

The MICs of all antibiotics were determined by microdilution broth procedure as recommended by National Committee of Clinical Laboratory Standards (NCCLS) guidelines.[1] Differences in MIC values were considered significant only when the dilution is more than a factor of 2 apart. Zone sizes were measured with a Fisher Zone Reader, and antibiotic concentrations were calculated from the standard curve for the appropriate compound.

Reagents were generally purchased in the highest purity available and used without further purification except otherwise stated. Azithromycin (**3**)[2], telithromycin (**4**)[3] and cethromycin

(**5**)[4] were synthesized in-house according to literature procedures and their *in vitro* evaluation were performed to allow direct comparison with 15-membered azalides presented in this paper.

Determination of Activities of Selected Compounds as Inibitors of DNA Gyrase, Topo IV and Bacterial Protein Synthesis

Protein translation inhibition by the selected compounds was determined with a coupled transcription/translation assay by using *E. coli* S30 extracts for circular DNA with the pBestLuc plasmid (Promega), according to the manufacturer's protocol. After pre-incubation for 10 min, the translation reactions were initiated by adding 0.1 μg of plasmid DNA and incubated at 37°C for 50 min. The reactions were then stopped by cooling in ice, 15 μL was added to luciferase assay reagent (50 μL, Promega), and the luminescence was measured with a Tecan plate reader.

Inhibitory activities of selected compounds on *E. coli* DNA gyrase and topoisomerase IV were evaluated by published procedures.[5,6] DNA gyrase activity was quantified in a supercoiling assay using relaxed pBR322 DNA and supercoiled pBR322 DNA was used for the topoisomerase IV relaxation assay. The IC_{50} for gyrase supercoiling was visually assessed as the concentration of compound, which led to a 50% reduction of the supercoiled band and a spread of topoisomerase above. The IC_{50} for relaxation was determined visually, as being the compound concentration at which the relaxed band was reduced by 50% and a supercoiled band with topoisomers appeared.

Experimental Procedures

4”-O-Allylazithromycin 11,12-cyclic carbonate (5)

To a solution of 2’-O-acetyl azithromycin-11,12-cyclic carbonate **4** (0.408 g, 0.5 mmoL) in dry THF (4 mL) under an atmosphere of nitrogen was added tetrakistriphenylphosphine palladium (0.057 g, 0.05 mmol) and allyl t-butyl carbonate (0.30 g, 1.9 mmoL). The resulting mixture was stirred under reflux. After 3 h of reflux TLC indicated 90% conversion of the desired product. The solvent was evaporated and the crude product dissolved in 4 mL of methanol. The mixture was stirred overnight at reflux and then concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel eluting with E1 system (90:9:0.5; dichloromethane/MeOH/aq. NH_3) to yield 0.24 g (70%) of a pale yellow crystals. HRMS (ES) calcd for $C_{42}H_{74}N_2O_{13}$ (MH^+) 815.5191, found 815.5185. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (1H, 4”-$OCH_2\underline{CH}CH_2$), 5.22 (1H, 4”-$OCH_2CH\underline{CH_{2a}}$), 5.10 (1H, 4”-$OCH_2CH\underline{CH_{2b}}$), 4.82 (1H, H-1"), 4.76 (1H, H-13), 4.39 (1H, H-1'), 4.27 (1H, H-11), 4.24 - 4.14 (2H, H-5", H-3), 4.03 (2H, 4”-$O\underline{CH_2}CHCH_2$), 3.67 (1H, H-5'), 3.40 (1H, H-5), 3.25 (3H, 3"-OMe), 3.15 (1H, H-10), 3.00 (1H, H-2'), 2.90 (1H, H-4"), 2.75 (1H, H-2), 2.45-2.30 (2H, H-3', H-9a), 2.27-2.20 (2H, H-2"b, H-9b), 2.17 (6H, 3'-NMe_2), 2.12 (3H, 9a-NMe), 2.02 (1H, H-9b), 1.90-1.85 (3H, H-4, H-7b, H-8), 1.75 (1H, H-14b), 1.59 (1H, H-14a), 1.55-1.50 (2H, H-4'b, H-2"a), 1.47 (3H, 12-Me), 1.40 (1H, H-7a), 1.22 (3H, 5"-Me), 1.18-1.15 (6H, 6-Me, 3"-Me), 1.13 (3H, 2-Me), 1.09 (1H, H-4'a), 1.03 (3H, 5'-Me), 0.99-0.94 (6H, 4-Me, 10-Me), 0.89 (3H, 8-Me), 0.86 (3H, 15-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1 (C-1), 152.5 (11,12-C=O), 135.6 (4”-$OCH_2\underline{CH}CH_2$), 115.7 (4”-$OCH_2CH\underline{CH_2}$), 102.0 (C-1'), 94.8 (C-1"), 86.0 (C-4"), 85.5 (C-11), 84.9 (C-12), 82.7 (C-5), 77.1 (C-3), 75.3 (C-13), 74.4 (4”-$O\underline{CH_2}CHCH_2$), 73.6 (C-6), 73.1 (C-3"), 70.6 (2C; C-2', C-5'), 66.6 (C-9), 64.8 (C-3'), 64.0 (C-5"), 59.6 (C-10), 47.9 (3"-OMe), 44.8 (C-2), 41.7 (C-4), 41.0 (C-7), 40.3 (3'-NMe_2), 34.6 (C-2"), 34.0 (9a-

NMe), 30.5 (C-4'), 27.4 (6-Me), 25.3 (C-8), 22.5 (8-Me), 21.9 (5'-Me), 21.4 (C-14), 21.1 (3"-Me), 18.7 (5"-Me), 14.8 (2-Me), 13.6 (12-Me), 10.5 (C-15), 9.2 (4-Me), 5.5 (10-Me). Anal. Calcd. For $C_{42}H_{74}N_2O_{13}$: C, 61.89; H, 9.15; N, 3.44. Found: C, 62.05; H, 9.38; N, 3.23.

4”-O-(2-Oxo-ethoxy)-azithromycin 11,12-cyclic carbonate (6)

To a solution of 4”-O-allylazithromycin-11,12-cyclic carbonate (**5**) (0.20g, 0.23 mmoL) in THF (1mL) and water (1mL) was added osmium tetraoxide (2.0 mL of a 2.5% solution in THF). After stirring for 5 minutes sodium periodate (0.213 g, 1 mmoL) was added in one portion. The mixture was vigorously stirred for 3h at 25°C before being quenched with saturated aqueous Na_2SO_3 (10mL). The resulting solution was stirred at 25°C for 2 h and then partitioned between EtOAc (22 mL) and water (5.0 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (K_2CO_3), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, E1) provided the corresponding aldehyde **6** as a bright yellow solid (ca. 160 mg; 81% yield). HRMS (ES) calcd for $C_{41}H_{72}N_2O_{14}$ (MH^+) 817.4984, found 817.4992. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (1H, CH=O), 4.82 (1H, H-1"), 4.74 (1H, H-13), 4.45 (2H, 4”-OCH_2) 4.37 (1H, H-1'), 4.24 (1H, H-11), 4.22 - 4.12 (2H, H-5", H-3), 3.62 (1H, H-5'), 3.44 (1H, H-5), 3.23 (3H, 3"-OMe), 3.16 (1H, H-10), 2.99 (1H, H-2'), 2.89 (1H, H-4"), 2.73 (1H, H-2), 2.40-2.30 (2H, H-3', H-9a), 2.25-2.20 (2H, H-2"b, H-9b), 2.15 (6H, 3'-NMe_2), 2.11 (3H, 9a-NMe), 2.03 (1H, H-9b), 1.92-1.83 (3H, H-4, H-7b, H-8), 1.77 (1H, H-14b), 1.60 (1H, H-14a), 1.58-1.52 (2H, H-4'b, H-2"a), 1.45 (3H, 12-Me), 1.42 (1H, H-7a), 1.20 (3H, 5"-Me), 1.17-1.13 (6H, 6-Me, 3"-Me), 1.11 (3H, 2-Me), 1.08 (1H, H-4'a), 1.05 (3H, 5'-Me), 1.00-0.95 (6H, 4-Me, 10-Me), 0.88 (3H, 8-Me), 0.76 (3H, 15-Me). Anal. Calcd. For $C_{41}H_{72}N_2O_{14}$: C, 60.27; H, 8.88; N, 3.43. Found: C, 60.56; H, 9.15; N, 3.38.

Reductive amination. General procedure.

a) Reductive amination with $NaBH_3CN$

4"-O-{2-[4-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-piperazin-1-yl]-ethoxy}-azithromycin 11,12-cyclic carbonate (7b)

Aldehyde **6** (114.4 mg, 0.14 mmoL) was dissolved in 0.9 mL of methanol. Three molar equivalents of 1-ethyl-4-oxo-6-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid (126.6 mg, 0.42 mmoL) was added as a 1 M solution in methanol (0.42 mL), followed by 0.43 mL of 1 M solution of acetic acid in methanol. The pH was checked and adjusted to about 6 with acetic acid, if necessary. $NaCNBH_3$ was added as a freshly prepared 0.3 M solution in methanol (0.19 mL), and the mixture was stirred at room temperature for 3 h. The reaction was quenched with a few drops of water and concentrated under reduced pressure. The residue was purified by silica gel chromatography (1-5% MeOH/0.5-1% triethylamine/ dichloromethane) to give 100.3 mg (75 %) of the title product as a yellow solid. HRMS (ES) calcd for $C_{57}H_{91}N_5O_{16}$ (MH^+) 1102.6461, found 1102.6446. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.20 (s, 1H), 7.85 (d, 1H), 7.40 (s, 1H), 5.26 (d, 1H), 4.70 (d, 1H), 4.65 (d, 1H), 4.55 (d, 1H), 4.44 (m, 1H), 4.25 (s, 1H), 4.20 (m, 2H), 3.76 (m, 1H), 3.68 (s, 1H), 3.57 (d, 1H), 3.31 (bs, 3H+2H), 3.28 (t, 1H), 3.01 (t, 2H), 3.00 (t, 2H), 2.76 (m, 1H), 2.68 (m, 1H), 2.56 (m, 1H), 2.54 (d, 1H), 2.43 (d, 1H), 2.33 (s, 6H), 2.29 (s, 3H), 2.05 (t, 1H), 2.02 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.75 (d, 1H), 1.75 (d, 1H), 1.66 (dd, 1H), 1.53 (t, 3H), 1.45 (m, 1H), 1.27 (s, 3H), 1.24 (m, 1H), 1.20 (d, 3H), 1.19 (d, 3H), 1.18 (d, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.08 (d, 3H), 1.04 (d, 3H), 0.90 (d, 3H), 0.89 (t, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 178.8, 172.3, 167.9, 153.1, 152.3, 146.7, 141.5, 128.1, 116.6, 114.3, 107.6, 102.2, 94.5, 94.2, 82.9, 78.8, 77.6, 77.4, 74.2, 73.6, 73.5, 72.8, 70.8, 69.9, 67.7, 65.4, 62.9, 62.5, 49.4, 49.2, 47.4, 45.2, 44.3, 42.4, 42.1, 40.3, 36.3, 34.9, 34.2, 29.4, 27.6, 26.6, 21.8, 21.7, 21.3, 21.3, 17.6, 16.1, 14.3, 14.4, 11.5, 8.9, 7.1. Anal. Calcd. For $C_{57}H_{91}N_5O_{16}$: C, 62.10; H, 8.32; N,

6.35. Found: C, 62.18; H, 8.37; N, 6.09.

The compounds **7a** and **7e** were prepared according to the same general procedure as for the synthesis of **7b**. **7a**: HRMS (ES) calcd for $C_{59}H_{95}N_5O_{16}$ (MH^+) 1130.6774, found 1130.6778. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.24 (s, 1H), 7.90 (d, 1H), 7.45 (s, 1H), 5.20 (d, 1H), 4.73 (d, 1H), 4.66 (d, 1H), 4.59 (d, 1H), 4.48 (m, 1H), 4.20-3.77 (m, 6H), 3.64 (s, 1H), 3.54 (d, 1H), 3.31 (bs, 5H), 3.17 (m, 1H), 3.04-2.73 (m, 5H), 2.68-2.54 (m, 2H), 2.50 (d, 1H), 2.40 (d, 1H), 2.30 (s, 6H), 2.25 (s, 3H), 2.10 (t, 1H), 2.03-1.92 (m, 3H), 1.79 (d, 1H), 1.76 (d, 1H), 1.64 (dd, 1H), 1.55 (t, 3H), 1.45 (m, 1H), 1.28 (s, 3H), 1.25 (t, 3H), 1.23 (m, 1H), 1.21 (d, 3H), 1.20 (d, 3H), 1.17 (d, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.07 (d, 3H), 1.05 (d, 3H), 0.93 (d, 3H), 0.90 (t, 3H). Anal. Calcd. For $C_{59}H_{95}N_5O_{16}$: C, 62.69; H, 8.47; N, 6.20. Found: C, 63.03; H, 8.63; N, 6.11.

7e: HRMS (ES) calcd for $C_{58}H_{92}FN_5O_{17}$ (MH^+) 1150.6472, found 1150.6479. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.94 (d, 1H), 7.00 (d, 1H), 5.22 (d, 1H), 4.71 (d, 2H), 4.57 (d, 1H), 4.41 (m, 1H), 4.24 (s, 1H), 3.80 (m, 1H), 3.67 (s, 1H), 3.60 (d, 1H), 3.52 (m, 1H), 3.37 (m, 2H), 3.32 (s, 3H), 3.25 (m, 1H), 3.06 (m, 2H), 2.98 (m, 2H), 2.75 (m, 1H), 2.73 (m, 1H), 2, 71 (m, 1H), 2.64 (m, 2H), 2.56 (d, 1H), 2.45 (s, 6H), 2.42 (d, 1H), 2.33 (s, 3H), 2.07 (t, 1H), 2.04 (m, 1H), 2.00 (m, 1H), 1.91 (m, 1H), 1.73 (d, 1H), 1.65 (dd, 1H), 1.46 (m, 1H), 1.37 (m, 2H), 1.28 (s, 3H), 1.20 (d, 3H), 1.19 (d, 3H), 1.17 (d, 3H), 1.14 (d, 3H), 1.12 (s, 2x3H), 1.03 (d, 3H), 0.91 (d, 3H), 0.89 (t, 3H). Anal. Calcd. For $C_{58}H_{92}FN_5O_{17}$: C, 60.56; H, 8.06; N, 6.09. Found: C, 60.79; H, 8.33; N, 5.84.

b) Reductive amination with formic acid

4”-O-{2-[2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-

ethylamino]-ethoxy}-azithromycin 11,12-cyclic carbonate (7c)

A solution of aldehyde **6** (955.9 mg, 1.17 mmoL), 6-(2-amino-ethylamino)-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (563.1 mg, 1.75 mmoL), and 22.5 mL of EtOAc was heated to 70°C with stirring. Formic acid (58.9 mg, 1.28 mmoL) was added dropwise to the solution, and the temperature was lowered to 65°C. Stirring and heating was continued for 5 h. After cooling to room temperature, the reaction solution was washed twice with 25 mL portions of saturated aqueous $NaHCO_3$ and then once with 20 mL of saturated aqueous NaCl. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to furnish crude product as a yellow foam. This material was taken up in 100 mL of hot Et_2O; insolubles were filtered and saved. The filtrate was treated with 30 mL of hot hexane, and again the resulting insoluble matter was filtered and saved. The filtrate was concentrated to about 7.5 mL by boiling off excess solvent. The resulting solution was allowed to cool to room temperature and then cooled to 5°C for several hours. This procedure resulted in a formation of colorless precipitate (630.6 mg). The filtrate was combined with the insolubles that were saved, and the mixture was then chromatographed on silica gel. Elution with 9:1 CH_2Cl_2-MeOH containing 1% NH_4OH afforded an additional product (420.3 mg, 80% overall yield). HRMS (ES) calcd for $C_{56}H_{88}ClN_5O_{16}$ (MH^+) 1122.5915, found 1122.5920. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (1H, Q-2), 8.05 (1H, Q-5), 7.53 (1H, Q-8), 5.29 (1H, NH), 5.04 (1H, H-1''), 4.88 (1H, H-13), 4.53 (1H, H-1'), 4.42 (2H, H-11, H-3), 4.21 (1H, H-5''), 3.81-3.67 (2H, 4''-O$\underline{CH_2}CH_2$N), 3.64 (m, 1H, Q-CHcyclopropyl), 3.62 (1H, H-5'), 3.60 (1H, H-5), 3.34 (3H, 3''-OMe), 3.00 (1H, H-2'), 2.97 (2H, 4''-OCH$_2\underline{CH_2}$N), 2.86 (2H, H-2, H-10), 2.81 (1H, H-4''), 2.72 (1H, H-3'), 2.38 (1H, H-9b), 2.27 (6H, 3'-NMe_2), 2.24 (1H, H-2''b), 2.20 (3H, 9a-NMe), 2.08 (1H, H-9a), 1.93 (1H, H-8), 1.90-1.86 (1H, H-4), 1.83-1.78 (2H, H-4', H-14b), 1.71 (1H, H-4'b), 1.57-1.51 (3H, H-2''a, H-14a, H-7b), 1.42 (3H, 12-Me), 1.40 (2H, Q-CH_2cyclopropyl), 1.36 (1H, H-7a), 1.28

(3H, 5''-Me), 1.25 (6H, 3''-Me, 6-Me), 1.24 (2H, Q-CH_2cyclopropyl), 1.20 (3H, 5'-Me), 1.16 (3H, 2-Me), 1.03 (3H, 10-Me), 0.95 (3H, 4-Me), 0.92 (3H, 8-Me), 0.89 (3H, 15-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8 (C-1), 178.6 (Q-4), 167.2 (Q-COOH), 153.1 (11,12-C=O), 147.8 (Q-2), 140.9 (Q-6), 139.5 (Q-9), 134.9 (Q-7), 126.5 (Q-10), 126.2 (Q-5), 116.4 (Q-8), 108.5 (Q-3), 101.8 (C-1'), 94.8 (C-1''), 87.2 (C-4''), 85.8 (C-11), 84.6 (C-12), 83.1 (C-5), 76.8 (C-3), 75.8 (C-13), 73.7 (C-3''), 73.2 (C-6), 72.5 (4''-O$\underline{CH_2}CH_2$N), 71.4 (C-2'), 67.8 (C-5'), 67.5 (C-9), 64.2 (C-5''), 62.7 (C-3'), 60.8 (C-10), 49.1 (3''OMe), 44.3 (C-2), 43.5 (C-7), 40.8 (C-4), 40.4 (3'-NMe_2), 39.4 (4''-O$CH_2\underline{CH_2}$N), 35.4 (Q-CHcyclopropyl), 35.1 (C-2''), 34.0 (9a-NMe), 30.7 (C-4'), 26.3 (6-Me), 25.9 (C-8), 21.8 (8-Me), 21.6 (C-14), 21.5 (C-3''), 21.3 (C-5'), 18.1 (5''-Me), 14.4 (2-Me), 13.5 (12-Me), 11.3 (4-Me), 10.0 (15-Me), 8.3 (2C, Q-CH_2cyclopropyl), 4.7 (10-Me). Anal. Calcd. For $C_{56}H_{88}ClN_5O_{16}$: C, 59.91; H, 7.90; N, 6.24. Found: C, 60.16; H, 7.91; N, 6.02.

c) Reductive amination with $NaBH(OAc)_3$

4''-O-{2-[2-(3-carboxy-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylamino]-ethoxy}-azithromycin 11,12-cyclic carbonate (7d)

To a magnetically stirred solution of aldehyde **6** (2.17 g, 2.65 mmoL) in 8 mL of methanol was added 7-(2-amino-ethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (1.62 g, 5.3 mmol). After being stirred at room temperature for 30 min, the solution was treated with 0.15 mL (2.65 mmoL) of HOAc and cooled to 0°C. $NaBH(OAc)_3$ (563.4 mg, 2.66 mmoL) dissolved in MeOH (2 mL) was then added over a period of 10 min. Stirring and cooling was continued for 10 min. The reaction mixture was worked up and the crude product was chromatographed on silica gel to furnish 1.99 g (68%) of the above product. HRMS (ES) calcd for $C_{56}H_{88}FN_5O_{16}$ (MH^+) 1106.6210, found 1106.6209. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.93 (d, 1H), 7.00 (d, 1H), 5.24 (d, 1H), 4.70 (d, 2H), 4.55

(d, 1H), 4.40 (m, 1H), 4.24 (s, 1H), 3.80 (m, 1H), 3.66 (s, 1H), 3.61 (d, 1H), 3.51 (m, 1H), 3.36 (m, 2H), 3.31 (s, 3H), 3.24 (m, 1H), 3.05 (m, 2H), 2.99 (m, 2H), 2.74 (m, 1H), 2.74 (m, 1H), 2.71 (m, 1H), 2.63 (m, 2H), 2.55 (d, 1H), 2.46 (s, 6H), 2.43 (d, 1H), 2.34 (s, 3H), 2.08 (t, 1H), 2.05 (m, 1H), 2.01 (m, 1H), 1.92 (m, 1H), 1.74 (d, 1H), 1.65 (dd, 1H), 1.45 (m, 1H), 1.36 (m, 2H), 1.27 (s, 3H), 1.21 (d, 3H), 1.18 (d, 3H), 1.16 (d, 3H), 1.12 (d, 3H), 1.10 (s, 2x3H), 1.03 (d, 3H), 0.92 (d, 3H), 0.89 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 172.3, 167.5, 152.9, 148.7, 146.8, 142.72, 140.4, 115.8, 110.0, 107.8, 102.2, 96.0, 94.7, 83.4, 79.1, 77.8, 74.3, 73.7, 73.5, 73.0, 71.0, 70.0, 67.7, 65.6, 63.1, 62.7, 49.5, 47.5, 45.3, 44.5, 42.2, 42.1, 40.5, 36.3, 35.4, 34.9, 34.5, 29.9, 27.5, 26.8, 22.0, 21.7, 21.4, 17.8, 16.3, 14.5, 11.3, 9.2, 8.3, 7.4. Anal. Calcd. For $C_{56}H_{88}FN_5O_{16}$: C, 60.80; H, 8.02; N, 6.33. Found: C, 61.10; H, 8.26; N, 6.15.

4”-O-(2-{2-[2-(3-Carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethoxy]-ethylamino}-ethoxy)-azithromycin 11,12-cyclic carbonate (7f)

Starting from aldehyde **6** (100 mg, 0.122 mmoL) and 6-[2-(2-amino-ethoxy)-ethylamino]-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (222.9 mg, 0.61 mmoL) according to the general procedure for reductive amination with $NaBH_3CN$ 72.6 mg (51 %) of the title compound was obtained. HRMS (ES) calcd for $C_{58}H_{92}ClN_5O_{17}$ (MH^+) 1166.6177, found 1166.6160. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.15 (d, 1H), 6.89 (s, 1H), 5.30 (t, 1H) 5.24 (d, 1H), 4.72 (d, 1H), 4.71 (d, 1H), 4.55 (d, 1H), 4.42 (m, 1H), 4.24 (s, 1H), 3.76 (m, 1H), 3.67 (s, 1H), 3.62 (d, 1H), 3.45 (m, 1H), 3.30 (s, 3H), 3.26 (m, 2H), 3.20 (m, 1H), 2.95 (t, 2H), 2.78 (m, 1H), 2.73 (t, 2H), 2.69 (m, 1H), 2.62 (t, 1H), 2.58 (t, 1H), 2.53 (m, 2H), 2.40 (d, 1H), 2.32 (s, 3H+6H), 2.09 (t, 1H), 2.02 (m, 1H), 1.99 (m, 1H), 1.91 (m, 1H), 1.82 (m, 2H), 1.76 (d, 1H), 1.69 (m, 3H), 1.64 (dd, 1H), 1.48 (m, 1H), 1.35 (m, 2H), 1.30 (s, 3), 1.26 (d, 1H), 1.24 (d, 1H), 1.20 (d, 3H), 1.18 (d, 3H), 1.16 (d, 3H), 1.10 (s, 3H),

1.08 (s, 3H), 1.07 (d, 3H), 1.05 (d, 3H), 0.93 (d, 3H), 0.89 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 177.0 , 167.8, 152.9, 152.2, 146.9, 143.7, 127.8, 115.9, 114.3, 107.6, 102.3, 94.8, 94.5, 82.9, 78.9, 77.6, 77.4, 74.1, 73.6, 73.4, 72.8, 70.9, 69.9, 67.8, 65.5, 62.9, 62.5, 49.4, 49.0, 45.2, 44.8, 43.2, 42.3, 42.1, 42.3, 36.1, 34.9, 34.8, 34.2, 28.9, 27.5, 27.3, 26.7, 26.4, 21.9, 21.8, 21.4, 21.2, 17.7, 16.1, 14.4, 11.2, 8.9, 8.1, 7.3. Anal. Calcd. For $C_{58}H_{92}ClN_5O_{17}$: C, 59.70; H, 7.95; N, 6.00. Found: C, 59.89; H, 8.20; N, 5.74.

4”-O-[2-(2-{2-[2-(3-Carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethoxy]-ethoxy}-ethylamino)-ethoxy]-azithromycin 11,12-cyclic carbonate (7g)

Starting from aldehyde **6** (100 mg, 0.122 mmoL) and 6-{2-[2-(2-aminoethoxy)-ethoxy]-ethylamino}-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (250.0 mg, 0.61 mmoL) according to the general procedure for reductive amination with $NaBH_3CN$ 66.4 mg (45 %) of the title compound was obtained. HRMS (ES) calcd for $C_{60}H_{96}ClN_5O_{18}$ (MH^+) 1210.6439, found 1210.6426. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.25 (d, 1H), 6.91 (s, 1H), 5.31 (t, 1H), 5.25-4.74 (d, 2H), 4.64 (d, 1H), 4.50 (d, 1H), 4.42 (m, 1H), 4.26 (s, 1H), 3.76-3.67 (m, 1H + s, 1H), 3.66 (d, 1H), 3.48 (t, 2H), 3.43 (m, 1H), 3.43 (t, 2H), 3.30 (s, 3H), 3.26-3.20 (m, 3H), 2.97 (t, 2H), 2.75 (m, 1H), 2.76 (t, 2H), 2.65 (m, 1H), 2.60 (t, 1H), 2.57 (t, 1H), 2.52 (m, 2H), 2.42 (d, 1H), 2.31 (s, 3H+6H), 2.08 (t, 1H), 2.01-1.91 (m, 3H), 1.81 (m, 2H), 1.74 (d, 1H), 1.69 (m, 3H), 1.63 (dd, 1H), 1.45-1.35 (m, 3H), 1.32 (s, 3H), 1.27 (d, 1H), 1.25 (d, 1H), 1.21 (d, 3H), 1.19 (d, 3H), 1.15 (d, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.06 (d, 3H), 1.04 (d, 3H), 0.94 (d, 3H), 0.88 (t, 3H). Anal. Calcd. For $C_{60}H_{96}ClN_5O_{18}$: C, 59.51; H, 7.99; N, 5.78. Found: C, 59.75; H, 8.10; N, 5.46.

LiOH hydrolysis of cyclic carbonates. General procedure.

4”-O-{2-[4-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-piperazin-1-yl]-ethoxy}-

azithromycin (8b)

To a solution of 4”-{2-[4-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-piperazin-1-yl]-ethoxy}-azithromycin 11,12-cyclic carbonate **7b** (1.101 g, 1.0 mmoL) in THF-water mixture (1:1, 10.0 mL) was added LiOH (192 mg, 4.6 mmoL), and the resulting reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the solid was azeotroped with toluene (5 x 5 mL) and finally dried under vacuum. The acid salt was dissolved in water and the resulting solution was made acidic by dropwise addition of 2M aqueous HCl. The precipitate was filtered off to give 688.9 mg (64 %) of the title product as colorless solid. HRMS (ES) calcd for $C_{56}H_{93}N_5O_{15}$ (MH^+) 1076.6668, found 1076.6688. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.32 (s, 1H), 7.69 (d, 1H), 7.59 (d, 1H), 5.25 (d, 1H), 4.75 (d, 1H), 4.63 (d, 1H), 4.56 (d, 1H), 4.45 (m, 1H), 4.29 (s, 1H), 4.26 (m, 2H), 3.86 (m, 1H), 3.72 (m, 1H), 3.65 (s, 1H), 3.58 (d, 1H), 3.30 (bs, 5H), 3.28-3.01 (t, 1H+2H), 2.95 (t, 2H), 2.75 (m, 1H), 2.63 (m, 1H), 2.56 (m, 1H), 2.52-2.41 (d, 2H), 2.30 (s, 6H), 2.27 (s, 3H), 2.06 (t, 1H), 2.02 (m, 1H), 2.00-1.93 (m, 2H), 1.75-1.73 (d, 2H), 1.67 (dd, 1H), 1.55 (t, 3H), 1.48 (m, 1H), 1.28 (s, 3H), 1.25 (m, 1H), 1.21 (d, 3H), 1.19 (d, 3H), 1.18 (d, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 1.09 (d, 3H), 1.02 (d, 3H), 0.93 (d, 3H), 0.89 (t, 3H). Anal. Calcd. For $C_{56}H_{93}N_5O_{15}$: C, 62.49; H, 8.71; N, 6.51. Found: C, 62.51; H, 8.74; N, 6.44.

4”-O-{2-[2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethylamino]-ethoxy}-azithromycin (8c)

Starting from 4”-{2-[2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethylamino]-ethoxy}-azithromycin 11,12-cyclic carbonate **7c** (504.9 mg, 0.45 mmoL) according to the general procedure for LiOH hydrolysis 399.8 mg (81%) of the title compound was obtained. HRMS (ES) calcd for $C_{55}H_{90}ClN_5O_{15}$ (MH^+) 1096.6122, found

1096.6117. ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.06 (s, 1H), 7.52 (s, 1H), 5.39 (t, NH), 5.20 (d, 1H), 4.69 (d, 2H), 4.57 (d, 1H), 4.40 (m, 1H), 4.27 (s, 1H), 3.79 (m, 1H), 3.66 (s, 1H), 3.57 (d, 1H), 3.53 (m, 1H), 3.39 (m, 2H), 3.30 (s, 3H), 3.22 (m, 1H), 3.01 (t, 2H), 2.95 (m, 2H), 2.73 (m, 1H), 2.68 (m, 1H), 2.60 (m, 1H), 2.57 (m, 1H), 2.51 (m, 2H), 2.40 (d, 1H), 2.31 (s, 6H), 2.28 (s, 3H), 2.05 (t, 1H), 2.00 (m, 1H), 1.95 (m, 1H), 1.90 (m, 1H), 1.76 (d, 1H), 1.70 (d, 1H), 1.66 (dd, 1H), 1.47 (m, 1H), 1.40 (m, 2H), 1.28 (s, 3H), 1.25 (m, 1H), 1.23 (m, 2H), 1.20 (d, 3H), 1.18 (d, 3H), 1.15 (d, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.08 (d, 3H), 1.03 (d, 3H), 0.95 (d, 3H), 0.87 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 179.3, 172.5, 167.5, 145.9, 143.3, 133.1, 127.9, 126.5, 117.9, 107.3, 104.8, 102.0, 94.8, 83.1, 79.1, 77.8, 74.2, 73.8, 73.5, 72.9, 70.9, 70.2, 67.9, 65.6, 63.1, 62.7, 49.5, 47.6, 45.4, 44.4, 42.8, 42.60, 42.1, 40.4, 36.3, 35.4, 34.9, 34.5, 29.0, 27.7, 26.8, 22.0, 21.8, 21.5, 21.3, 17.9, 16.4, 14.4, 11.3, 9.0, 8.1, 7.4. Anal. Calcd. For $C_{55}H_{90}ClN_5O_{15}$: C, 60.23; H, 8.27; N, 6.39. Found: C, 60.50; H, 8.28; N, 6.12.

4”-O-{2-[2-(3-carboxy-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylamino]-ethoxy}-azithromycin (8d)

Starting from 4”-{2-[2-(3-carboxy-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylamino]-ethoxy}-azithromycin 11,12-cyclic carbonate **7d** (686.3 mg, 0.62 mmoL) according to the general procedure for LiOH hydrolysis 671.1 mg (75%) of the title compound was obtained. HRMS (ES) calcd for $C_{55}H_{90}FN_5O_{15}$ (MH^+) 1080.6417, found 1080.6420. ^{1}H-NMR ($CDCl_3$) δ 8.88 (s, 1H), 7.91 (d, 1H), 6.98 (d, 1H), 5.02 (d, 1H), 4.67 (d, 2H), 4.55 (d, 1H), 4.43 (m, 1H), 4.15 (s, 1H), 3.89 (m, 1H), 3.71 (s, 1H), 3.63 (d, 1H), 3.50 (m, 1H), 3.39 (m, 2H), 3.30 (s, 3H), 3.26 (m, 1H), 3.10 (m, 2H), 2.88 (m, 2H), 2.77 (m, 1H), 2.73 (m, 1H), 2.71 (m, 1H), 2.63 (m, 2H), 2.58 (d, 1H), 2.48 (s, 6H), 2.40 (d, 1H), 2.36 (s, 3H), 2.12 (t, 1H), 2.07 (m, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.71 (d, 1H), 1.66 (dd, 1H), 1.47 (m, 1H), 1.40 (m, 2H), 1.30 (s, 3H), 1.22 (d, 3H), 1.19 (d, 3H), 1.16 (d, 3H), 1.12 (d, 3H),

1.10 (s, 2x3H), 1.02 (d, 3H), 0.93 (d, 3H), 0.88 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 179.0, 173.3, 167.8, 148.9, 146.9, 142.3, 140.8, 116.0, 110.0, 107.9, 102.3, 96.3, 94.8, 83.0, 79.1, 77.8, 74.3, 73.6, 73.5, 73.2, 71.1, 70.0, 67.8, 65.7, 63.2, 62.7, 49.6, 47.8, 45.4, 44.2, 42.8, 42.5, 40.4, 36.3, 35.6, 34.9, 34.5, 30.03, 27.7, 26.5, 22.2, 21.4, 21.3, 17.9, 16.3, 14.6, 11.3, 9.3, 8.4, 7.5. Anal. Calcd. For $C_{55}H_{90}FN_5O_{15}$: C, 61.15; H, 8.40; N, 6.48. Found: C, 61.50; H, 8.79; N, 6.15.

4”-O-(2-{2-[2-(3-Carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethoxy]-ethylamino}-ethoxy)-azithromycin (8f)

Starting from 4”-(2-{2-[2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethoxy]-ethylamino}-ethoxy)-azithromycin 11,12-cyclic carbonate **7f** (20.0 mg, 0.02 mmoL) according to the general procedure for LiOH hydrolysis 11.7 mg (60 %) of the title compound was obtained. HRMS (ES) calcd for $C_{57}H_{94}ClN_5O_{16}$ (MH^+) 1140.6384, found 1140.6376. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.35 (d, 1H), 6.99 (s, 1H), 5.33 (t, 1H) 5.26 (d, 1H), 4.75 (d, 1H), 4.70 (d, 1H), 4.62 (d, 1H), 4.46 (m, 1H), 4.32 (s, 1H), 3.82-3.72 (m, 2H), 3.65 (s, 1H), 3.59 (d, 1H), 3.48 (m, 1H), 3.28 (s, 3H), 3.24-3.20 (m, 3H), 2.98 (t, 2H), 2.77 (m, 1H), 2.75 (t, 2H), 2.68 (m, 1H), 2.61 (t, 1H), 2.57 (t, 1H), 2.51 (m, 2H), 2.45 (d, 1H), 2.33 (s, 3H+6H), 2.11 (t, 1H), 2.02-1.99 (m, 2H), 1.92-1.80 (m, 3H), 1.78 (d, 1H), 1.72 (m, 3H), 1.67 (dd, 1H), 1.48-1.35 (m, 3H), 1.32 (s, 3H), 1.28 (d, 1H), 1.25 (d, 1H), 1.20 (d, 3H), 1.16 (d, 3H), 1.14 (d, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 1.05 (d, 3H), 1.02 (d, 3H), 0.91 (d, 3H), 0.88 (t, 3H). Anal. Calcd. For $C_{57}H_{94}ClN_5O_{16}$: C, 60.01; H, 8.31; N, 6.14. Found: C, 60.23; H, 8.36; N, 6.01.

4”-O-[2-(2-{2-[2-(3-Carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethoxy]-ethoxy}-ethylamino)-ethoxy]-azithromycin (8g)

Starting from 4”-[2-(2-{2-[2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin -6-ylamino)-ethoxy]-ethoxy}-ethylamino)-ethoxy]-azithromycin 11,12-cyclic carbonate **7g** (10.7 mg, 0.009 mmoL) according to the general procedure for LiOH hydrolysis 8.9 mg (85%) of the title compound was obtained. HRMS (ES) calcd for $C_{59}H_{98}ClN_5O_{17}$ (MH^+) 1184.6646, found 1184.6640. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.28 (d, 1H), 6.94 (s, 1H), 5.34 (t, 1H), 5.25-4.78 (m, 2H), 4.76-4.50 (m, 2H), 4.44 (t, 1H), 4.28 (s, 1H), 3.79 (m, 1H), 3.78-3.63 (m, 1H + s, 1H), 3.58 (d, 1H), 3.52 (t, 2H), 3.48 (m, 1H), 3.45 (t, 2H), 3.29 (s, 3H), 3.27-3.18 (m, 3H), 3.10 (t, 2H), 2.85 (m, 1H), 2.79 (t, 2H), 2.67 (m, 1H), 2.63 (t, 1H), 2.57 (t, 1H), 2.50 (m, 2H), 2.40 (d, 1H), 2.30 (s, 3H+6H), 2.09 (t, 1H), 2.01 (m, 1H), 1.91 (m, 2H), 1.84 (m, 2H), 1.75 (d, 1H), 1.68 (m, 3H), 1.65 (dd, 1H), 1.46-1.36 (m, 3H), 1.30 (s, 3H), 1.28 (d, 1H), 1.24 (d, 1H), 1.20 (d, 3H), 1.18 (d, 3H), 1.16 (d, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 1.06 (d, 3H), 1.04 (d, 3H), 0.95 (d, 3H), 0.89 (t, 3H). Anal. Calcd. For $C_{59}H_{98}ClN_5O_{17}$: C, 59.81; H, 8.34; N, 5.91. Found: C, 59.95; H, 8.39; N, 5.99.

The following compounds were also prepared by using the same general procedure:

8a: HRMS (ES) calcd for $C_{58}H_{97}N_5O_{15}$ (MH^+) 1104.6981, found 1104.6983. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.28 (s, 1H), 7.93 (d, 1H), 7.52 (s, 1H), 5.25 (d, 1H), 4.83 (d, 1H), 4.68 (d, 1H), 4.57 (d, 1H), 4.52 (m, 1H), 4.25-3.80 (m, 6H), 3.68 (s, 1H), 3.52 (d, 1H), 3.33-3.17 (m, 6H), 3.11-2.52 (m, 7H), 2.54 (d, 1H), 2.44 (d, 1H), 2.32 (s, 6H), 2.29 (s, 3H), 2.12 (t, 1H), 2.05-1.90 (m, 3H), 1.85 (d, 1H), 1.78 (d, 1H), 1.60 (m, 1H), 1.53 (t, 3H), 1.45 (m, 1H), 1.29 (s, 3H), 1.26 (t, 3H), 1.24 (m, 1H), 1.20 (d, 3H), 1.18 (d, 3H), 1.16 (d, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.07 (d, 3H), 1.04 (d, 3H), 0.96 (d, 3H), 0.89 (t, 3H). Anal. Calcd. For $C_{58}H_{97}N_5O_{15}$: C, 63.08; H, 8.85; N, 6.34. Found: C, 63.39; H, 8.90; N, 6.07.

8e: HRMS (ES) calcd for $C_{57}H_{94}FN_5O_{16}$ (MH^+) 1124.6680, found 1124.6685. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.90 (d, 1H), 7.05 (d, 1H), 5.24 (d, 1H), 4.74 (d, 2H), 4.52-4.41

(m, 2H), 4.26-3.83 (m, 1H), 3.70 (s, 1H), 3.63 (d, 1H), 3.55-3.35 (m, 2H), 3.33 (s, 3H), 3.25-2.96 (m, 5H), 2.75-2.60 (m, 5H), 2.54 (d, 1H), 2.44 (s, 6H), 2.39 (d, 1H), 2.33 (s, 3H), 2.10 (m, 1H), 2.02-1.89 (m, 3H), 1.75 (d, 1H), 1.65 (dd, 1H), 1.45-1.35 (m, 3H), 1.29 (s, 3H), 1.21 (d, 3H), 1.18 (d, 3H), 1.16 (d, 3H), 1.13 (d, 3H), 1.11 (s, 2x3H), 1.04 (d, 3H), 0.92 (d, 3H), 0.90 (t, 3H). Anal. Calcd. For $C_{57}H_{94}FN_5O_{16}$: C, 60.89; H, 8.43; N, 6.23. Found: C, 61.13; H, 8.52; N, 5.89.

4”-O-(3-Methoxycarbonyl-allyloxy)-azithromycin 11,12-cyclic carbonate (9)

A mixture of aldehyde **6** (587.6 mg, 0.719 mmoL) and stabilized ylide (360 mg, 1.08 mmoL, 1.5 mol equiv.) in benzene (7.2 mL) was heated at reflux for 3 h. After cooling to 25 °C, the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 90:9:0.5 CH_2Cl_2:MeOH:aq. NH_3) furnished unsaturated methylester (313.8 mg, 50%) as a mixture of E and Z isomers in 95:5 ratio according LC/MS analysis. HRMS (ES) calcd for $C_{44}H_{76}N_2O_{15}$ (MH^+) 873.5246, found 873.5238. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.95 (1H, dd, J= 15.8 Hz), 5.86 (1H, d, J= 15.8 Hz), 4.86 (d, 1H), 4.79 (dd, 1H), 4.42 (d, 1H), 4.24 (s, 1H), 4.24-4.17 (m, 2H), 4.09 (d, 2H), 3.70 (3H, s), 3.64 (m, 1H), 3.42 (d, 1H), 3.22 (s, 3H), 3.13 (m, 1H), 3.04 (dd, 1H), 2.88 (d, 1H), 2.79 (m, 1H), 2.42-2.34 (m, 2H), 2.28-2.23 (m, 2H), 2.23 (s, 6H), 2.15 (s, 3H), 2.03 (m, 1H), 1.91-1.87 (m, 3H), 1.75 (m, 1H), 1.56 (m, 1H), 1.54-1.52 (m, 2H), 1.45 (s, 3H), 1.42 (d, 1H), 1.21 (d, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 1.13 (d, 3H), 1.10 (m, 1H), 1.07 (d, 3H), 0.98 (d, 3H), 0.96 (d, 3H), 0.89 (d, 3H), 0.86 (t, 3H). Anal. Calcd. For $C_{44}H_{76}N_2O_{15}$: C, 60.53; H, 8.77; N, 3.21. Found: C, 60.57; H, 8.81; N, 3.20.

4”-O-(3-Methoxycarbonyl-propoxy)-azithromycin 11,12-cyclic carbonate (10)

The mixture of unsaturated ester **9** (200 mg, 0.23 mmoL) was dissolved in MeOH (5 mL), treated with Pd/C (50 mg, 10 wt% Pd) and catalytically hydrogenated in Parr apparatus for 5

h. After filtration through a Celite pad, the filtrate was concentrated *in vacuo* and the residue purified by column chromatography (eluting with E1 system) to give 125 mg (62%) of pure ester as a colorless crystalline solid. HRMS (ES) calcd for $C_{44}H_{78}N_2O_{15}$ (MH^+) 875.5402, found 875.5380. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.88 (d, 1H), 4.76 (dd, 1H), 4.44 (d, 1H), 4.27 (s, 1H), 4.24 (m, 1H), 4.19 (m, 1H), 3.78 (d, 2H), 3.71 (3H, s), 3.65 (m, 1H), 3.48 (d, 1H), 3.24 (s, 3H), 3.19 (m, 1H), 3.04 (d, 1H), 2.83 (d, 1H), 2.74 (m, 1H), 2.45-2.31 (m, 2H), 2.32 (t, 2H), 2.30-2.21 (m, 2H), 2.25 (s, 6H), 2.17 (s, 3H), 2.04 (m, 1H), 1.94-1.84 (m, 3H), 1.88 (t, 2H), 1.73 (m, 1H), 1.62 (m, 1H), 1.58-1.51 (m, 2H), 1.48 (s, 3H), 1.45 (d, 1H), 1.23 (d, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 1.14 (d, 3H), 1.12 (m, 1H), 1.08 (d, 3H), 0.99 (d, 3H), 0.95 (d, 3H), 0.88 (d, 3H), 0.85 (t, 3H). Anal. Calcd. For $C_{44}H_{78}N_2O_{15}$: C, 60.39; H, 8.98; N, 3.20. Found: C, 60.61; H, 9.20; N, 2.89.

4”-O-(3-Carboxy-propoxy)-azithromycin (11)

To a solution of ester **10** (875 mg, 1.0 mmoL) in 1:1 THF-water (10.0 mL) at room temperature was added LiOH (192 mg, 4.57 mmoL), and the resulting reaction mixture was stirred at the same temperature for 12h. The solvent was removed under reduced pressure, and the solid was azeotroped with benzene (5x5 mL) and finally dried under vacuum. The acid salt was dissolved in water and the resulting solution was made acidic by dropwise addition of 2M aqueous HCl. The precipitate was filtered of to give 787 mg (90%) of pure title compound. HRMS (ES) calcd for $C_{42}H_{78}N_2O_{14}$ (MH^+) 835.5453, found 835.5463. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.90 (d, 1H), 4.77 (dd, 1H), 4.35 (d, 1H), 4.21 (s, 1H), 4.27-4.15 (m, 2H), 3.71 (d, 2H), 3.60 (m, 1H), 3.43 (d, 1H), 3.24 (s, 3H), 3.16 (m, 1H), 3.06 (dd, 1H), 2.89 (d, 1H), 2.72 (m, 1H), 2.45-2.35 (m, 2H), 2.32 (t, 2H), 2.28-2.21 (m, 2H), 2.18 (s, 6H), 2.14 (s, 3H), 2.01 (m, 1H), 1.90-1.86 (m, 3H), 1.88 (t, 2H), 1.76 (m, 1H), 1.58 (m, 1H), 1.55-1.50 (m, 2H), 1.47 (s, 3H), 1.44 (d, 1H), 1.23 (d, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.14 (d, 3H), 1.12

(m, 1H), 1.08 (d, 3H), 0.98 (d, 3H), 0.96 (d, 3H), 0.88 (d, 3H), 0.85 (t, 3H). Anal. Calcd. For $C_{42}H_{78}N_2O_{14}$: C, 60.41; H, 9.41; N, 3.35. Found: C, 60.53; H, 9.45; N, 3.30.

HBTU coupling. General procedure.

4”-O-{3-[2-(3-Carboxy-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylcarbamoyl]-propoxy}-azithromycin (12 d)

DIPEA (201.4 μL, 1.4 mol. equiv.) was added dropwise via syringe at 0°C to a solution of azithromycin-4”-butane-carboxylic acid **11** (181.7 mg, 0.22 mmoL) and HBTU (81.7 mg, 0.22 mmoL) in dry DMF (2.6 mL). The mixture was stirred for 15 min before 7-(2-amino-ethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (48.8 mg, 0.16 mmoL) was added over a period of 30 min. The reaction mixture was stirred at room temperature overnight (20 h), and then diluted with water (30 mL). The aqueous phase was extracted twice with EtOAc (2x50 mL), and the combined organic phases were washed sequentially with saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). Drying with Na_2SO_4 and evaporation afforded 127.5 mg (71%) of 4”-{3-[2-(3-carboxy-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylcarbamoyl]-propoxy}-azithromycin (**12d**) as a colorless solid. HRMS (ES) calcd for $C_{57}H_{92}FN_5O_{16}$ (MH^+) 1122.6523, found 1122.6529. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.70 (s, 1H), 7.94 (s, 1H), 7.00 (d, 1H) 4.89 (d, 1H), 4.77 (dd, 1H), 4.46 (d, 1H), 4.32 (s, 1H), 4.27 (m, 1H), 4.21 (m, 1H), 3.88 (d, 2H), 3.75 (3H, s), 3.71 (m, 1H), 3.65 (m, 1H), 3.51 (d, 1H), 3.29 (s, 3H), 3.10 (m, 1H), 3.00 (d, 1H), 2.87 (d, 1H), 2.81 (m, 1H), 2.48-2.38 (m, 2H), 2.31 (t, 2H), 2.28-2.21 (m, 2H), 2.19 (s, 6H), 2.16 (s, 3H), 2.01 (m, 1H), 1.95 (m, 1H), 1.86 (m, 2H), 1.80 (t, 2H), 1.75 (m, 1H), 1.62 (m, 1H), 1.56-1.50 (m, 2H), 1.47 (s, 3H), 1.44 (d, 1H), 1.42 (m, 2H), 1.25 (m, 2H), 1.21 (d, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 1.14 (d, 3H), 1.11 (m, 1H), 1.05 (d, 3H), 0.98 (d, 3H), 0.96 (d, 3H),

0.89 (d, 3H), 0.87 (t, 3H). Anal. Calcd. For $C_{57}H_{92}FN_5O_{16}$: C, 61.00; H, 8.26; N, 6.24. Found: C, 61.36; H, 8.50; N, 5.86.

4”-O-{3-[2-(3-Carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethylcarbamoyl]-propoxy}-azithromycin (12c)

Starting from intermediate **11** (834 mg, 1.0 mmoL) and 6-(2-amino-ethylamino)-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (234.9 mg, 0.73 mmoL) 620.5 mg (75 %) of the title compound was obtained. HRMS (ES) calcd for $C_{57}H_{92}ClN_5O_{16}$ (MH^+) 1138.6228, found 1138.6229. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.73 (s, 1H), 8.05 (s, 1H), 7.53 (d, 1H), 5.29 (t, NH), 4.89 (d, 1H), 4.78 (dd, 1H), 4.52 (d, 1H), 4.42 (s, 1H), 4.32 (m, 1H), 4.25 (m, 1H), 3.92 (d, 2H), 3.78 (3H, s), 3.72 (m, 1H), 3.68 (m, 1H), 3.50 (d, 1H), 3.15 (s, 3H), 3.05 (m, 1H), 2.91 (d, 1H), 2.84 (d, 1H), 2.77 (m, 1H), 2.66-2.42 (m, 2H), 2.35 (t, 2H), 2.30-2.20 (m, 2H), 2.17 (s, 6H), 2.15 (s, 3H), 1.99 (m, 1H), 1.91 (m, 1H), 1.85 (m, 2H), 1.79 (t, 2H), 1.76-1.60 (m, 2H), 1.55-1.49 (m, 2H), 1.46 (s, 3H), 1.41 (d, 1H), 1.34 (m, 2H), 1.25 (m, 2H), 1.20 (d, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 1.13 (d, 3H), 1.09 (m, 1H), 1.04 (d, 3H), 0.99 (d, 3H), 0.95 (d, 3H), 0.90 (d, 3H), 0.86 (t, 3H). Anal. Calcd. For $C_{57}H_{92}ClN_5O_{16}$: C, 60.12; H, 8.14; N, 6.15. Found: C, 60.33; H, 8.27; N, 6.05.

According to the above general procedure following 4”-O-ether linked azithromycin derivatives with quinolone side chain were also prepared: **12a**, **12b**, **12e**, **12f**, and **12g**.

12a: HRMS (ES) calcd for $C_{60}H_{99}N_5O_{16}$ (MH^+) 1146.7087, found 1146.7090. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.38 (s, 1H), 7.97 (d, 1H), 7.55 (s, 1H), 5.25 (d, 1H), 4.86 (d, 1H), 4.70 (d, 1H), 4.42 (d, 2H), 4.23-3.84 (m, 7H), 3.70 (s, 1H), 3.52 (d, 1H), 3.35-2.52 (m, 13H), 2.65 (d, 3H), 2.42 (d, 1H), 2.30 (s, 6H), 2.27 (s, 3H), 2.12 (t, 1H), 2.08-1.87 (m, 3H), 1.89 (d, 1H), 1.80 (d, 1H), 1.62 (m, 1H), 1.55 (t, 3H), 1.46 (m, 1H), 1.28 (s, 3H), 1.25 (t,

3H), 1.22 (m, 1H), 1.20 (d, 3H), 1.17 (d, 3H), 1.15 (d, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.06 (d, 3H), 1.03 (d, 3H), 0.98 (d, 3H), 0.90 (t, 3H). Anal. Calcd. For $C_{60}H_{99}N_5O_{16}$: C, 62.86; H, 8.70; N, 6.11. Found: C, 62.88; H, 8.86; N, 6.10.

12b: HRMS (ES) calcd for $C_{58}H_{95}N_5O_{16}$ (MH^+) 1118.6774, found 1118.6777. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (s, 1H), 8.31 (s, 1H), 7.65 (d, 1H), 7.63 (d, 1H), 5.30 (d, 1H), 4.77 (d, 1H), 4.65 (d, 1H), 4.54 (d, 1H), 4.49 (s, 1H), 4.40-3.70 (m, 5H), 3.63 (s, 1H), 3.52 (m, 1H), 3.30 (m, 4H), 3.27-3.03 (t, 1H+2H+2H), 2.98 (t, 2H), 2.72-2.54 (m, 3H), 2.44 (m, 4H), 2.30 (s, 6H), 2.20 (s, 3H), 2.04 (t, 1H), 2.02-1.90 (m, 3H), 1.74 (d, 2H), 1.67 (d, 1H), 1.57 (t, 3H), 1.48-1.35 (m, 3H), 1.28 (s, 3H), 1.24 (m, 1H), 1.20 (d, 3H), 1.18 (d, 3H), 1.16 (d, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 1.08 (d, 3H), 1.01 (d, 3H), 0.94 (d, 3H), 0.90 (t, 3H). Anal. Calcd. For $C_{58}H_{95}N_5O_{16}$: C, 62.29; H, 8.56; N, 6.26. Found: C, 62.36; H, 8.66; N, 6.20.

12e: HRMS (ES) calcd for $C_{59}H_{96}FN_5O_{17}$ (MH^+) 1166.6785, found 1166.6782. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 7.88 (d, 1H), 7.07 (d, 1H), 5.21 (d, 1H), 4.74 (d, 1H), 4.53-4.42 (m, 3H), 4.34-3.75 (m, 2H), 3.70 (m, 1H), 3.60 (d, 1H), 3.55-3.30 (m, 5H), 3.20-2.80 (m, 5H), 2.74-2.61 (m, 5H), 2.54 (d, 3H), 2.46 (m, 6H), 2.35 (m, 1H), 2.30 (s, 3H), 2.10 (m, 1H), 2.02-1.70 (m, 5H), 1.65 (d, 1H), 1.47-1.34 (m, 3H), 1.30 (s, 3H), 1.20 (d, 3H), 1.18 (d, 3H), 1.16 (d, 3H), 1.14 (d, 3H), 1.12 (s, 6H), 1.05 (d, 3H), 0.94 (d, 3H), 0.91 (t, 3H). Anal. Calcd. For $C_{59}H_{96}FN_5O_{17}$: C, 60.75; H, 8.30; N, 6.00. Found: C, 61.91; H, 8.34; N, 5.72.

12f: HRMS (ES) calcd for $C_{59}H_{96}ClN_5O_{17}$ (MH^+) 1182.6490, found 1182.6494. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 8.21 (d, 1H), 7.00 (s, 1H), 5.35 (m, 1H) 5.21 (d, 1H), 4.81 (d, 1H), 4.73 (d, 1H), 4.65 (d, 1H), 4.48-3.70 (m, 4H), 3.63 (s, 1H), 3.55 (d, 1H), 3.48-3.18 (m, 7H), 2.95 (t, 3H), 2.77-2.65 (m, 4H), 2.61-2.51 (m, 4H), 2.45 (m, 3H), 2.30 (s, 3H+6H), 2.10 (m, 1H), 2.03-1.79 (m, 5H), 1.75 (d, 1H), 1.72 (t, 3H), 1.60 (m, 1H), 1.50-1.39 (m, 4H), 1.30 (s, 3H), 1.27 (d, 1H), 1.24 (d, 1H), 1.19 (d, 3H), 1.17 (d, 3H), 1.15 (d, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.04 (d, 3H), 1.01 (d, 3H), 0.93 (d, 3H), 0.89 (t, 3H). Anal. Calcd. For

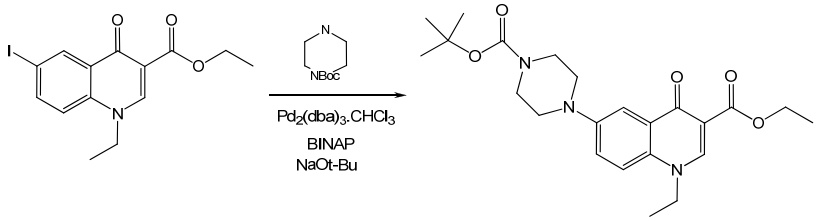
$C_{59}H_{96}ClN_5O_{17}$: C, 59.91; H, 8.18; N, 5.92. Found: C, 60.07; H, 8.37; N, 5.76.

12g: HRMS (ES) calcd for $C_{61}H_{100}ClN_5O_{18}$ (MH^+) 1226.6752, found 1226.6760. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 8.32 (d, 1H), 6.98 (s, 1H), 5.30 (t, 1H) 5.24-4.76 (m, 2H), 4.76-4.53 (m, 2H), 4.40 (t, 1H), 4.30 (s, 1H), 3.79 (m, 1H), 3.78-3.60 (m, 2H), 3.58 (m, 1H), 3.52-3.45 (m, 4H), 3.40 (t, 2H), 3.30 (s, 3H), 3.25-3.15 (m, 3H), 3.12 (t, 2H), 2.85-2.60 (m, 4H), 2.57 (t, 1H), 2.52 (m, 4H), 2.40 (d, 1H), 2.30 (s, 3H+6H), 2.10 (m, 1H), 2.01-1.80 (m, 5H), 1.74 (d, 1H), 1.68 (t, 3H), 1.65 (dd, 1H), 1.48-1.35 (m, 5H), 1.31 (s, 3H), 1.28 (d, 1H), 1.25 (d, 1H), 1.21 (d, 3H), 1.19 (d, 3H), 1.16 (d, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.06 (d, 3H), 1.04 (d, 3H), 0.97 (d, 3H), 0.90 (t, 3H). Anal. Calcd. For $C_{61}H_{100}ClN_5O_{18}$: C, 59.71; H, 8.22; N, 5.71. Found: C, 59.94; H, 8.57; N, 5.48.

Synthesis of 1-ethyl-4-oxo-6-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid (b).[7]

General Procedure for the Palladium-Catalyzed Arylation of Amines using BINAP/$Pd_2(dba)_3$.$CHCl_3$.

a) 6-(4-tert-Butoxycarbonyl-piperazin-1-yl)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

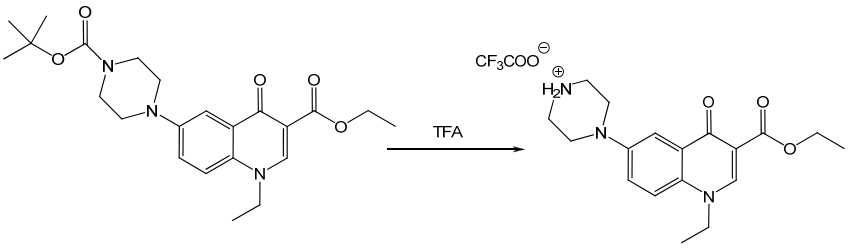


An oven-dried Pyrex flask was charged with sodium tert-butoxide (134.5 mg, 1.4 mmoL), $Pd_2(dba)_3.CHCl_3$ (2.3-9.2 mg, 0.0025-0.01 mmoL), and BINAP (4.7-18.7 mg, 0.0075-0.03 mmoL). The Pyrex tube was fitted with a septum, and the air atmosphere was replaced with argon, dry THF (3 mL), 6-iodo-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester[8] (371.2 mg, 1.0 mmoL), and Boc-piperazine (223.5 mg, 1.2 mmoL) were added by syringe. The reaction was heated to 80°C with stirring until starting material was consumed as

judged by LC-MS analysis. The reaction mixture was cooled to room temperature, diluted with diethyl ether (15 mL), filtered, and concentrated. The crude reaction mixture was then further purified by flash chromatography on silica gel to give 356.5 mg (83%) of the title compound as a pale yellow solid. MS (m/z) 430.2 (M^++1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H, Q), 8.22 (s, 1H, Q), 7.81 (m, 2H, Q), 4.42 (q, 2H, Q-N-$\underline{CH_2}CH_3$), 4.23 (q, 2H, Q-CO_2-$\underline{CH_2}CH_3$), 3.34 (dd, 8H, N$\underline{CH_2}\underline{CH_2}$N), 1.38 (s, 9H, t-BuOCO), 1.35 (t, 3H, Q-N-$CH_2\underline{CH_3}$), 1.28 (t, 3H, Q-CO_2-$CH_2\underline{CH_3}$). Anal. Calcd. For $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 64.44; H, 7.29; N, 9.63.

Hydrolysis of Boc-piperazin-1-ylquinolone-3-ethylcarboxylate with TFA.

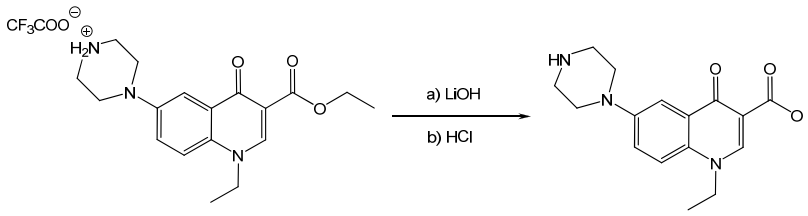
b) 1-Ethyl-4-oxo-6-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester trifluoroacetate



At 0°C, a solution of Boc protected quinolone (429.5 mg, 1.0 mmoL) in 10 mL of CH_2Cl_2 and trifluoroacetic acid (1:1) was stirred for 5 hours. The volatile materials were evaporated under reduced pressure, and the residue was triturated with diethylether and filtered. The resulting product (354.7 mg, 80%) was used without further purification in the next step. Anal. Calcd. For $C_{20}H_{23}F_3N_3O_5$: C, 54.30; H, 5.24; N, 9.50. Found: C, 54.44; H, 5.30; N, 9.45.

Hydrolysis of 1-ethyl-4-oxo-6-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester trifluoroacetate with LiOH.

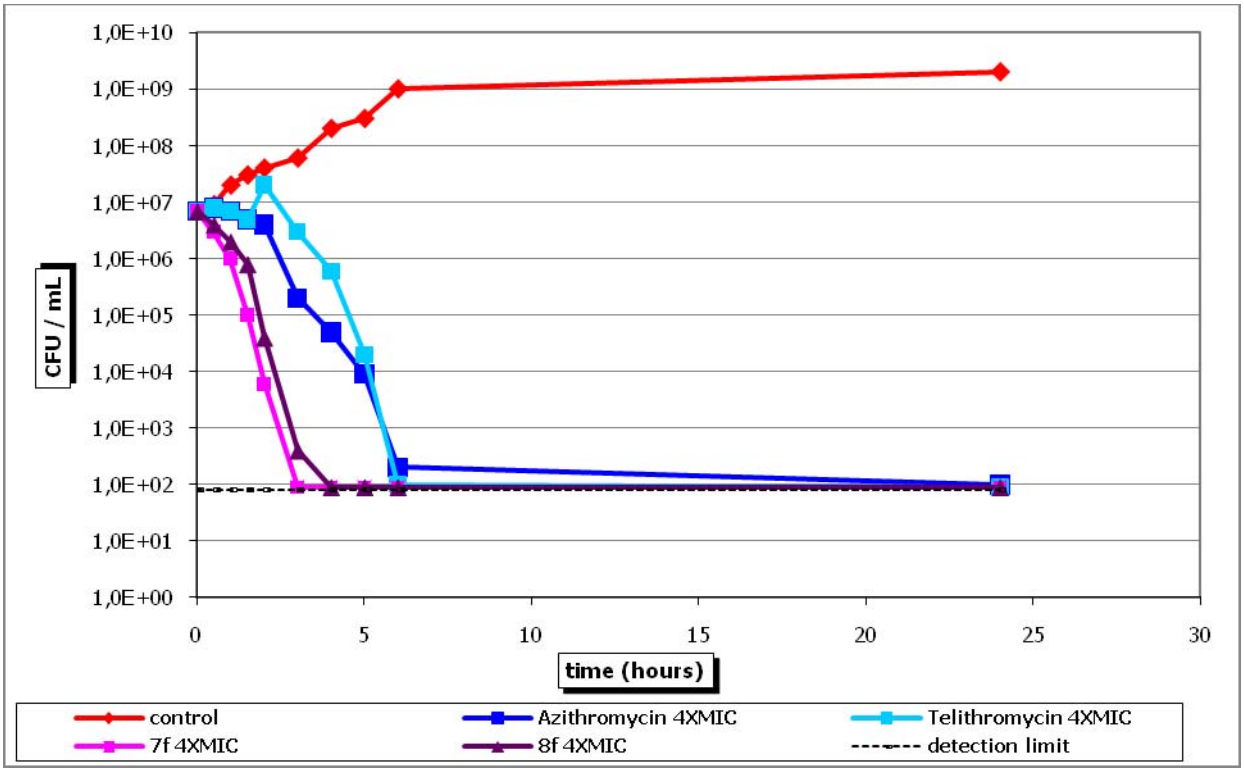
c) 1-Ethyl-4-oxo-6-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid (b)



To a solution of 1-ethyl-4-oxo-6-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester trifluoroacetate (486.6 mg, 1.1 mmoL) in THF-water mixture (1:1, 10.0 mL) was added LiOH (212.2 mg, 5.1 mmoL), and the resulting reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the solid was azeotroped with toluene (5 x 5 mL) and finally dried under vacuum. The salt was dissolved in water and the resulting solution was made acidic by dropwise addition of 2M aqueous HCl. The precipitate was filtered of to give 232.0 mg (70 %) of the title product as colorless solid. MS (m/z) 302.1 (M^++1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (s, 1H, Q), 8.20 (s, 1H, Q), 7.81 (m, 2H, Q), 4.43 (q, 2H, Q-N-$\underline{CH_2}CH_3$), 4.20 (q, 2H, Q-CO_2-$\underline{CH_2}CH_3$), 3.46 (t, 4H, N$\underline{CH_2}CH_2$NH), 2.78 (t, 4H, $NCH_2\underline{CH_2}$NH), 1.91 (bs, 1H, $NCH_2CH_2\underline{NH}$), 1.36 (s, 9H, $\underline{t\text{-}Bu}$OCO), 1.33 (t, 3H, Q-N-$CH_2\underline{CH_3}$), 1.26 (t, 3H, Q-CO_2-$CH_2\underline{CH_3}$). Anal. Calcd. For $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.92; H, 6.46; N, 13.80.

Table 2. Antibacterial activity of **7f** and **8f** against *H. influenzae*

Time hours	Control	Azithromycin 4xMIC	Telithromycin 4xMIC	7f 4xMIC	8f 4xMIC	Detection limit
0,0	7,0E+06	7,0E+06	7,0E+06	7,0E+06	7,0E+06	8,0E+01
0,5	9,0E+06	8,0E+06	8,0E+06	3,0E+06	4,0E+06	8,0E+01
1,0	2,0E+07	7,0E+06	7,0E+06	1,0E+06	2,0E+06	8,0E+01
1,5	3,0E+07	5,0E+06	5,0E+06	1,0E+05	8,0E+05	8,0E+01
2,0	4,0E+07	4,0E+06	2,0E+07	6,0E+03	4,0E+04	8,0E+01
3,0	6,0E+07	2,0E+05	3,0E+06	9,0E+01	4,0E+02	8,0E+01
4,0	2,0E+08	5,0E+04	6,0E+05	9,0E+01	9,0E+01	8,0E+01
5,0	3,0E+08	9,0E+03	2,0E+04	9,0E+01	9,0E+01	8,0E+01
6,0	1,0E+09	2,0E+02	1,0E+02	9,0E+01	9,0E+01	8,0E+01
24,00	2,0E+09	1,0E+02	9,0E+01	9,0E+01	9,0E+01	8,0E+01



CFU: colony-forming units

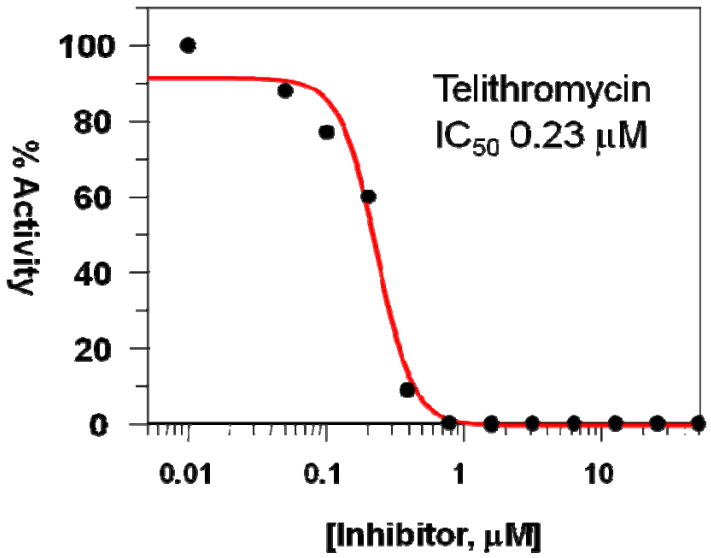
Compounds were tested at concentrations of 1, 4 and 10 x MIC. MIC values were:

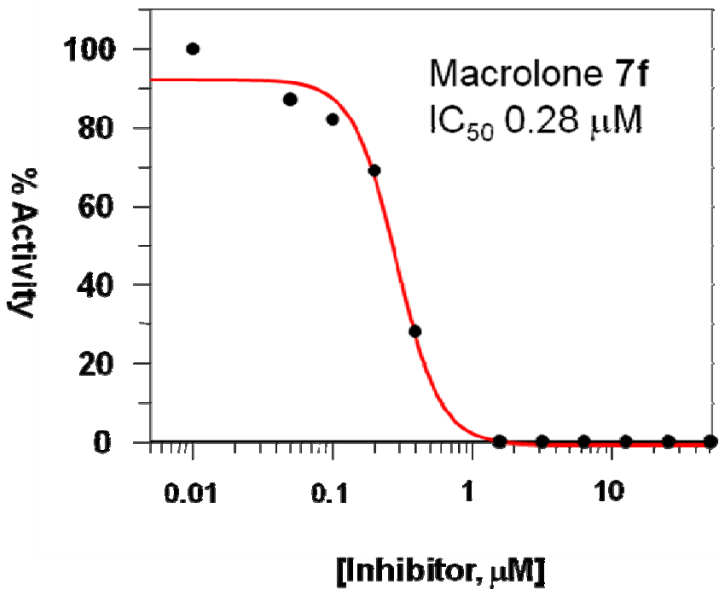
Compound	MIC (μg/mL)
Azithromycin	1
Telithromycin	1
7f	0.5
8f	0.5

Table 3. Activity of selected macrolones as inhibitors of DNA gyrase, Topo IV and bacterial protein synthesis

Comp	DNA gyrase[a] IC_{50} (μM)	Topo IV[b] IC_{50} (μM)	Protein Synthesis[c] IC_{50} (μM)
7f	70	60	0.28
8f	60	50	0.35
Telithromycin	>50	>50	0.23
Cipro	0.8	3.0	>50

[a]Supercoiling assay with *E. coli* DNA gyrase; [b]*E. coli* Topoisomerase IV relaxation assay; [c]In vitro transcription/translation assay with *E. coli* S30 extract system





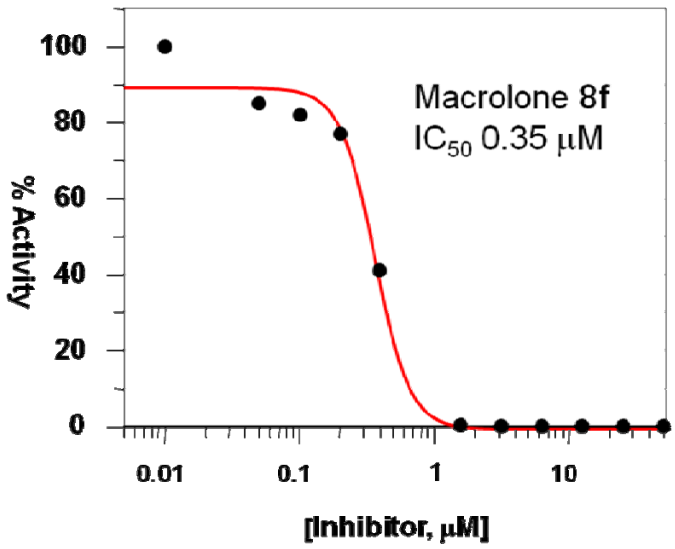


Figure 3. Semilogarithmic plots of protein synthesis inhibition measured for telithromycin, **7f**, and **8f**

Table 4. Antibacterial activity of quinolone analogues **a-g** [a]

Compound	*S. aureus*				*S. pneumoniae*			*S. pyogenes*				*M. cat.*[b]	*H. inf.*[c]
	Ery-S	iMLS	cMLS	M	Ery-S	cMLS	M	Ery-S	iMLS	cMLS	M		
a	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
b	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
c	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
d	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
e	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
f	>64	>64	64	>64	64	>64	>64	32	>64	>64	>64	>64	>64
g	>64	>64	64	>64	64	>64	>64	64	>64	>64	>64	>64	>64

[a] Minimum inhibitory concentration (MIC) values are given in µg/mL. [b] *M. catarrhalis*. [c] *H. influenzae*. Ery-S: erythromycin-susceptible strains; iMLS: inducible resistance to MLS antibiotics; cMLS: constitutive MLS resistance; M: efflux mediated macrolide resistance.

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