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Synthesis and antibacterial activity of new *N*-alkylammonium and carbonate-triazole derivatives within desosamine of 14- and 15-membered lactone macrolides

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Abstract: Desosamines of azithromycin (**AZM**) and clarithromycin (**CLA**) were modified *via* *N*-alkylation or nucleophilic substitution at carbonyl/CuAAC sequence. The biological studies revealed higher antibacterial potency of quaternary *N*-alkylammonium bromides of **CLA** as compared to **AZM**. SAR studies of **CLA** salts, including biological, conformation and molecular docking analysis, enriched by physico-chemical parameters, showed the importance of less bulky and unsaturated substituent for efficient docking mode at the ribosomal tunnel and good antibacterial potency against clinical and standard *Streptococcus pneumoniae* and *Streptococcus pyogenes* strains (MICs 0.25 or 0.5 μg/mL). These **CLA** salts have also at least a 3-fold lower cytotoxicity than the reference antibiotics at comparable antibacterial activity against *S. pneumoniae* clinical strain. Differences in antibacterial effects noted for **AZM** and **CLA** salts bearing less bulky *N*-substituents are better understandable when considering their binding modes in the ribosomal tunnel rather than their common low lipophilicity and excellent water solubility.

The term 'macrolide' was proposed by Robert Woodward as an abbreviation of macrolactone glycoside antibiotics, a class of natural products composed of macrocyclic lactones to which one or more deoxysaccharide residues were attached[1]. Nowadays, this term comprises not only macrocyclic compounds with lactone moieties, but also with lactam groups [2–9]. Macrolide antibiotics are a large group of natural products produced by various *Streptomyces* species. They are FDA approved and widely used against various infectious diseases, especially caused by Gram-positive and some selected Gram-negative bacteria species such as *Bordetella pertussis* and *Legionella pneumophila* [10–12]. Macrolides can by classified by a lot of different criteria like: type and size of the ring, type of saccharide moieties linked to the aglycone and by their source of origin [13–15]. The most known and widespread clinically used macrolides are: natural 14-membered Erythromycin A (**ERY**, **Figure 1**); its semisynthetic derivative – Clarithromycin (**CLA**, **Figure 1**), with a methoxy group in the aglycone at C(6) position; and Azithromycin (**AZM**, **Figure 1**), which belong to 15-membered lactone azalides. Due to the fast progressing bacteria resistance towards these medically useful lactone macrolides such as: **ERY**, **CLA** and **AZM**, their macrocyclic scaffolds can be templates for designing of their antibacterial efficient alternatives, containing structurally diverse pharmacophores.

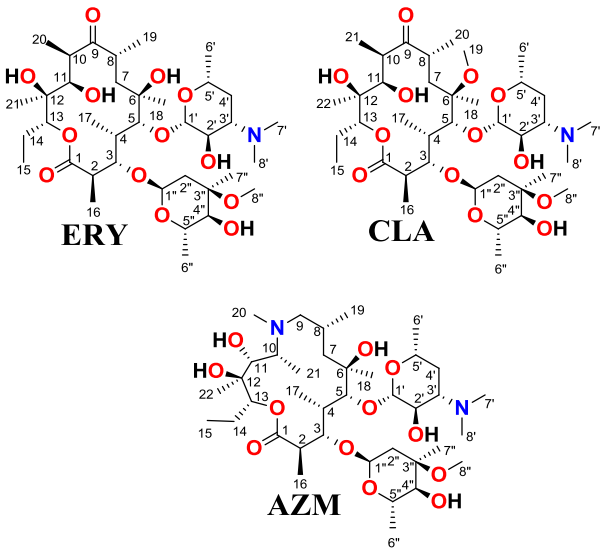


Figure 1. Examples of typical lactone macrolides: 14-memebered erythromycin (**ERY**) and clarithromycin (**CLA**) and 15-membered azithromycin (**AZM**).

Over the years hundreds of **ERY**, **CLA** and **AZM** modifications were carried out by various research groups[13,16–21]. Some of them have focused on modifications of the desosamine saccharide, which is a common part for these antibiotics and is thought to be crucial for molecular recognition between the macrolide and its binding site, located in ribosomal tunnel near the A2103*/A2045** nucleotide (**H. marismortuil*/**D. radiodurans*) of peptidyl transferase (PTC) loop, *via* H-bonding and hydrophobic interactions.[18] In the last 10 years, a few research groups modified the desosamine *N*,*N*-dimethylamine group *via* removal of the methyl or introduction of triazole motif, however, in these structures at least one proton was attached to the nitrogen of desosamine [22–25]. There were also attempts to modify the desosamine at the C-2' position *via* carbamoyl or chloroquinoline-alkyl ether arms [26–28]. Recently, an approach based on potentiators of the antibiotic activity of clarithromycin against *Escherichia coli* also have been tested.[29] To the best our knowledge all modifications of desosamine part have been unsuccessful with a significant decrease in antibacterial potency, where at the best case $MICs_{(S.\ pneumoniae,\ S.\ pyogenes)}$ were ≥ 8 μg/mL [30]. There are known several binding modes of the lactone macrolides at the ribosomal tunnel, what complicates a target-based designing of new antibacterial agents among these antibiotics [18]. Up to know, 1D and 2D NMR methods together with DFT theoretical approach have been successfully applied in conformational studies of 14- and 15-membered macrolides and their derivatives as well as in analysis of binding mode of these antibiotics to ribosomes.[31,32] Here we attempted to synthesize new decladinosyl **AZM** analogs, decorated with a carbonate-triazole motif within the desosamine saccharide. On the one hand, with the knowledge of different orientations of the lactone aglycones of macrolides at the binding site, we hypothesized that increased bulkiness and length of the desosamine arm would contribute to a reorientation of the macrolide aglycone. This leads to a better fit of the extended C(5)-arm into the tunnel lumen and would have an positive impact on antibacterial activity. On the other hand, it was postulated that the presence of a positively charged nitrogen atom within the desosamine of **CLA** and **AZM** is an important for transportation of the macrolide to the target site.[10] We introduced structurally diverse substituents at the nitrogen of the desosamine *via* S_N2 reaction to test the influence of these modifications on the binding mode and on the antibacterial potency. We also expected that introduction of the substituent at the desosamine nitrogen, having sp and sp^2 carbon atoms, could contribute to additional π-π stabilizing interactions in the ribosomal tunnel. Hence, in order to add an alternative antibacterial agents to the known **ERY**, **CLA** and **AZM** antibiotics, we developed new synthetic routes leading to *N*-alkylammonium and carbonate-triazole derivatives within the desosamine part of **CLA** and **AZM**.

Results and Discussion

Synthesis and structure of new macrolide derivatives

The S_N2 type *N*-alkylation reactions between 2'-*O*-acetyl azithromycin (**1**), decladinosyl azithromycin (**2**), azithromycin (**AZM**) and clarithromycin (**CLA**) and different alkyl bromides were performed in water-free acetonitrile solution. For **AZM**, however, there were two possible sites of *N*-alkylation: one at the nitrogen of desosamine and the second at the nitrogen of the aglycone (N9a). Our reaction conditions allowed to obtain solely *N*-alkylation products of **AZM** at the nitrogen of desosamine. This result can be partially explained by the predominant structure of **AZM** in solution, where the nitrogen of the aglycone (N9a) is involved in the intramolecular H-bond with the hydroxyl group O(6)H, what decreases the nucleophilicity and limits availability of this nitrogen for the reaction (please see below discussed structure of **AZM** in solution). This conclusion is supported by the highest chemical shift of O(6)H signal (~7.7 ppm) in ^{1}H NMR spectra, and the most red-shifted band, assigned to $\nu(O_6H)$ stretching vibrations (~2600 cm^{-1}) in FT-IR spectra of the macrolide derivatives (**Tables 1S**, **2S**, **5S**, **copies of FT-IR spectra** in **Supporting Information**). Hence, NMR and FT-IR results indicate that the O(6)H hydroxyl group is the strongest H-bonded as compared to the other hydroxyls in the lactone macrolides scaffolds. The structures of synthesized series of new *N*-alkylammonium **AZM** (**1e**, **1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e**-**3u**) and **CLA** (**4a**-**4e**, **4i**) salts are displayed in **Figure 2**. Yields of *N*-alkylation of **CLA** and **AZM** antibiotics after purification were in the range 76-98%. The decladinosyl **AZM** was synthesized from **AZM** treated with HCl solution, according to procedure described by Arsic et al.[33] The 2'-*O*-acetyl azithromycin was synthesized by the reaction between **AZM** and the acetic anhydride with 98% yield. For *N*-alkylammonium salts, terminated with the ester group, simultaneously with formation of **3g** and **3h** products, an unexpected cyclization took place affording a novel lactone by-product **3gh'** (**Figure 3**, **ESI** and **NMR data** - **Supporting Information**). Unfortunately, it was not possible to separate the mixtures of **3g** with **3gh'** and **3h** with **3gh'** *via* classical column chromatography due to the common, extremely polar character of these derivatives.

In turn, propargyl-carbonate decladinosyl azithromycin derivatives (**5x$_1$**-**x$_{18}$, Figure 4**) were synthesized in three steps. The first step was a hydrolysis of the cladinose of **AZM**, performed under the HCl treatment. The second step was the nucleophilic substitution at carbonyl taking place between hydroxyl O(2')H of decladinosyl azithromycin and acid chloride moiety of propargyl chloroformate. At the third step, Huisgen dipolar cycloadditions between **5** and 1.2 molar equiv. of respective azide, in the presence of 1.8 molar equiv. of ascorbic acid and 1.2 molar equiv. of copper (I) acetate, resulted in formation of the carbonate-triazole products exclusively as 1,4-regioisomers (**5x$_1$**-**x$_{18}$, Figure 4**). New carbonate-triazole derivatives of **AZM**, lacking of the cladinose, were purified by column chromatography with yields ranging from 15 to 50%.

Conformations of the new **AZM** derivatives of both types (**1e**, **1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e**-**3u, 5x$_1$**-**5x$_{18}$**; **Figures 2** and **4**) and *N*-alkylammonium salts of **CLA** (**4a**-**4e**, **4i**; **Figure 2**) were determined in details in $CDCl_3$ and in DMSO-d_6 solutions *via* 2D NMR studies (^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC methods). NMR analysis clearly indicated that in the case of **CLA** and **AZM** salts, the newly introduced substituent at the nitrogen of desosamine is oriented towards the cladinose side (**Figure 5a**). Such an orientation of the substituent, transferred into the bacteria ribosomes, would be perpendicular relative to the ribosomal tunnel lumen (**Figure 5a**). In turn, the conformation of the extended desosamine arm by carbonate-triazole linkage for **AZM** derivatives (**Figure 5b**) seems to be favorable regarding the direction of the arm relative to the target P-site at the ribosomal tunnel (parallel relative to the tunnel lumen). The lack of the cladinose saccharide in structures of derivatives **5x$_1$-5x$_{18}$** has a little impact on the conformation of the aglycone, if compared to that of **AZM** (**Figure 5b**).

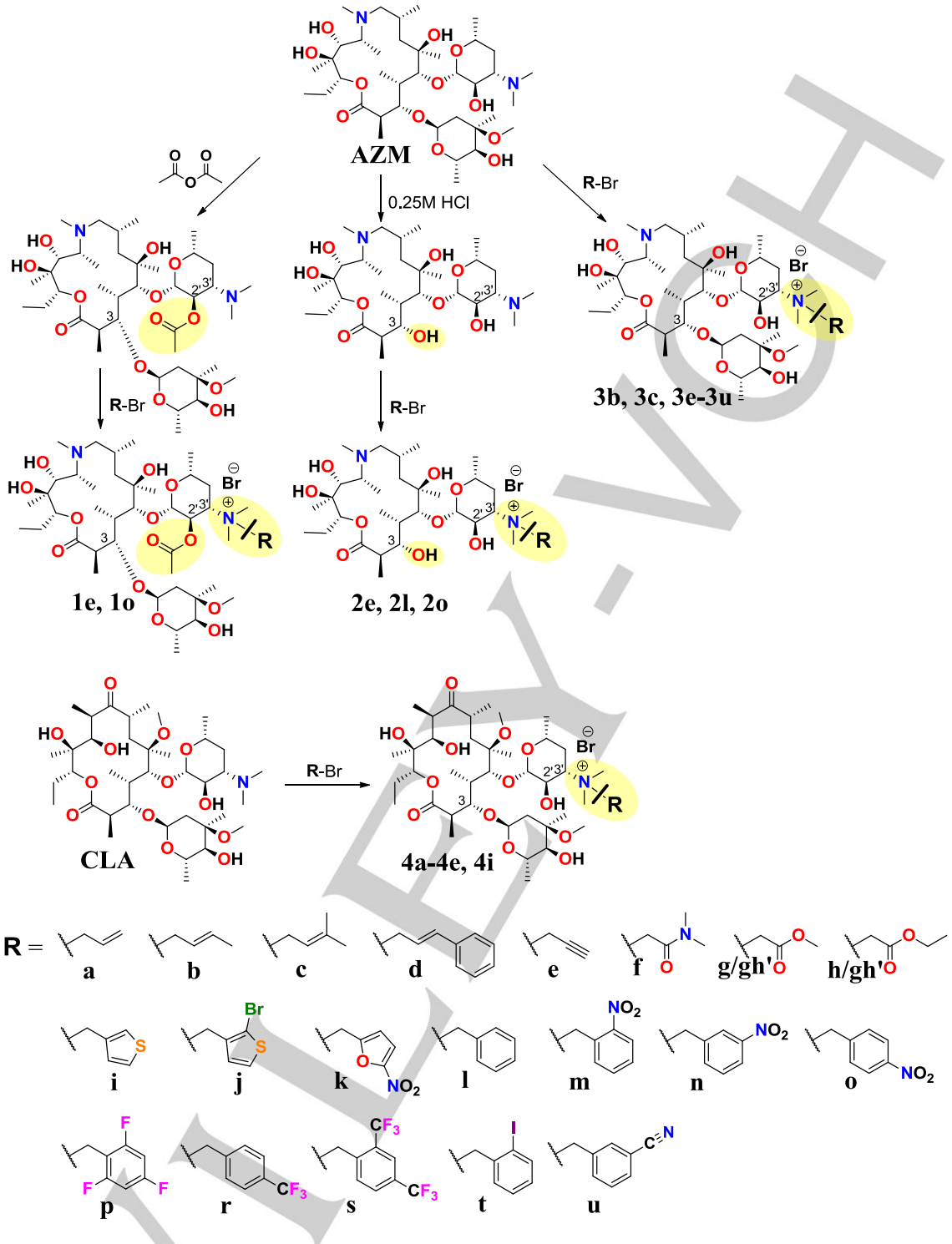


Figure 2. Synthesis of *N*-alkylammonium salts of **AZM** and **CLA** analogs.

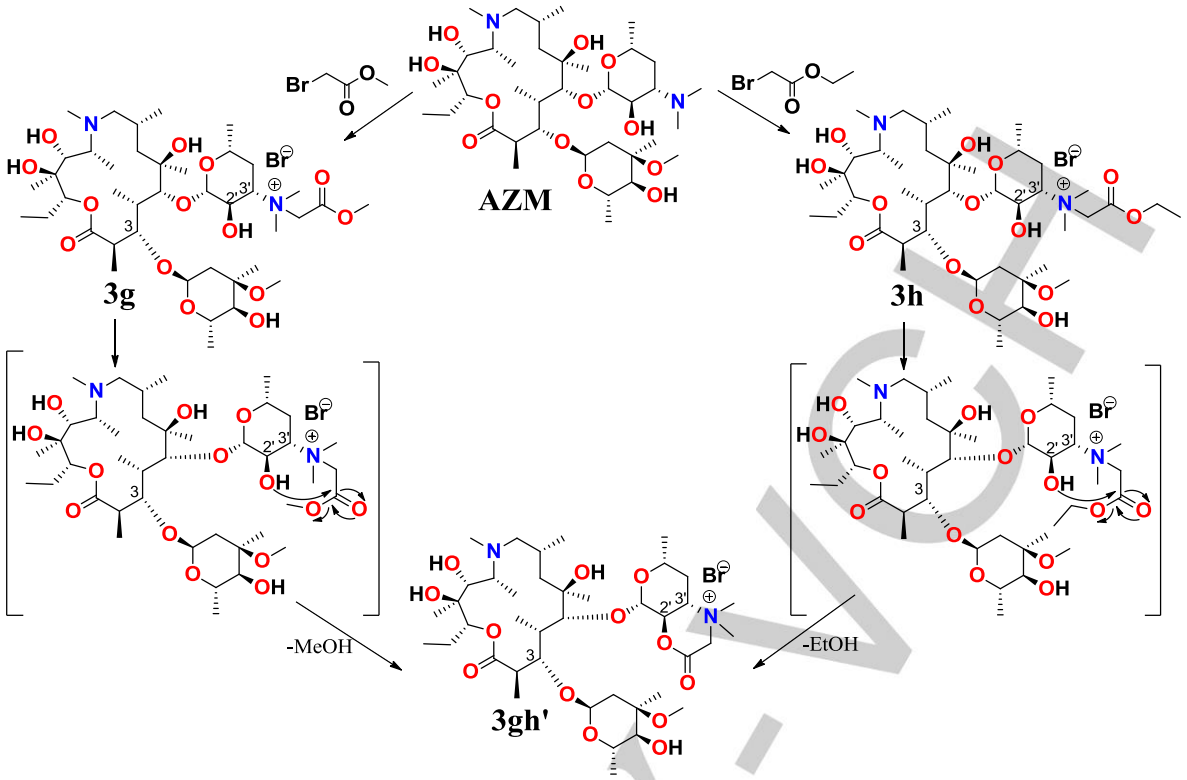


Figure 3. Unexpected cyclization process of *N*-alkylammonium ester-containing bromides, taking part within the desosamine and yielding inseparable mixture of newly formed lactone products **3gh'** with **3g** and **3h**.

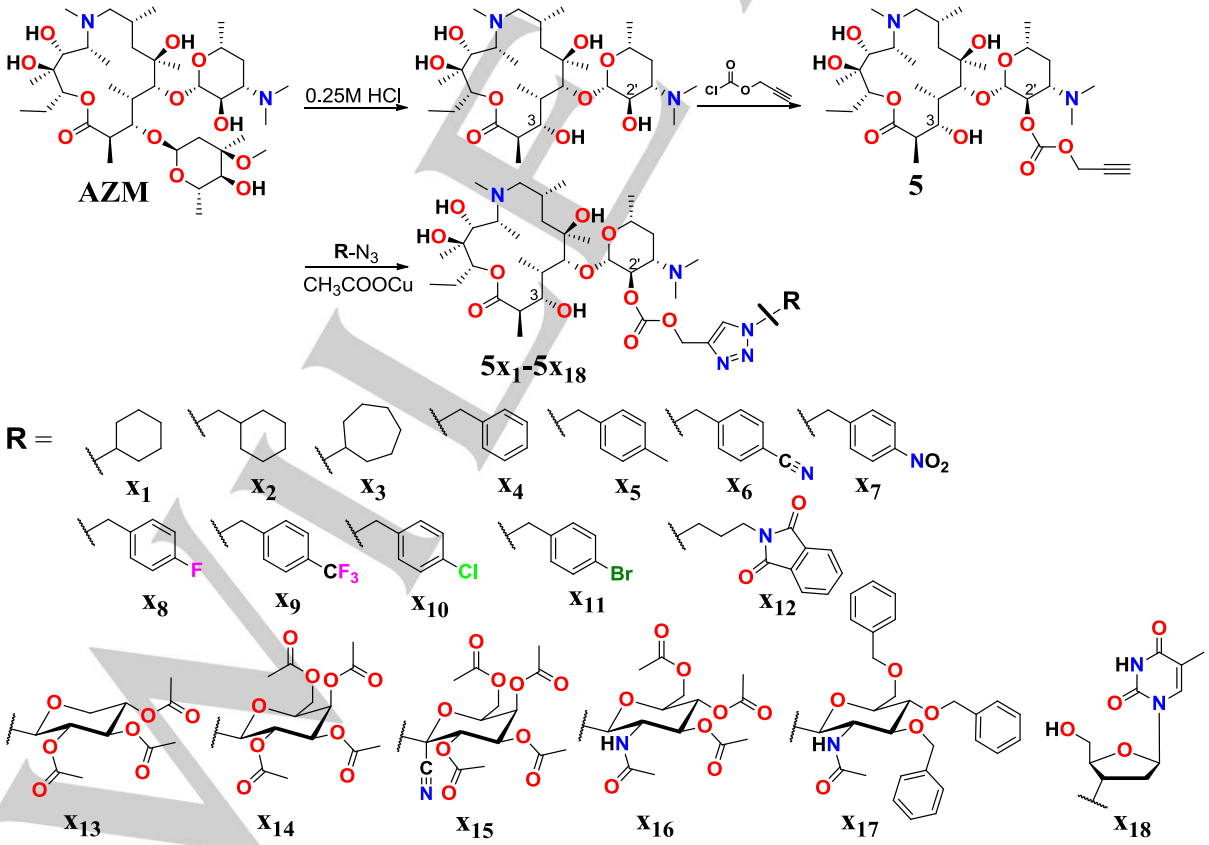


Figure 4. Synthesis of **AZM** carbonate-triazole macrolide analogs.

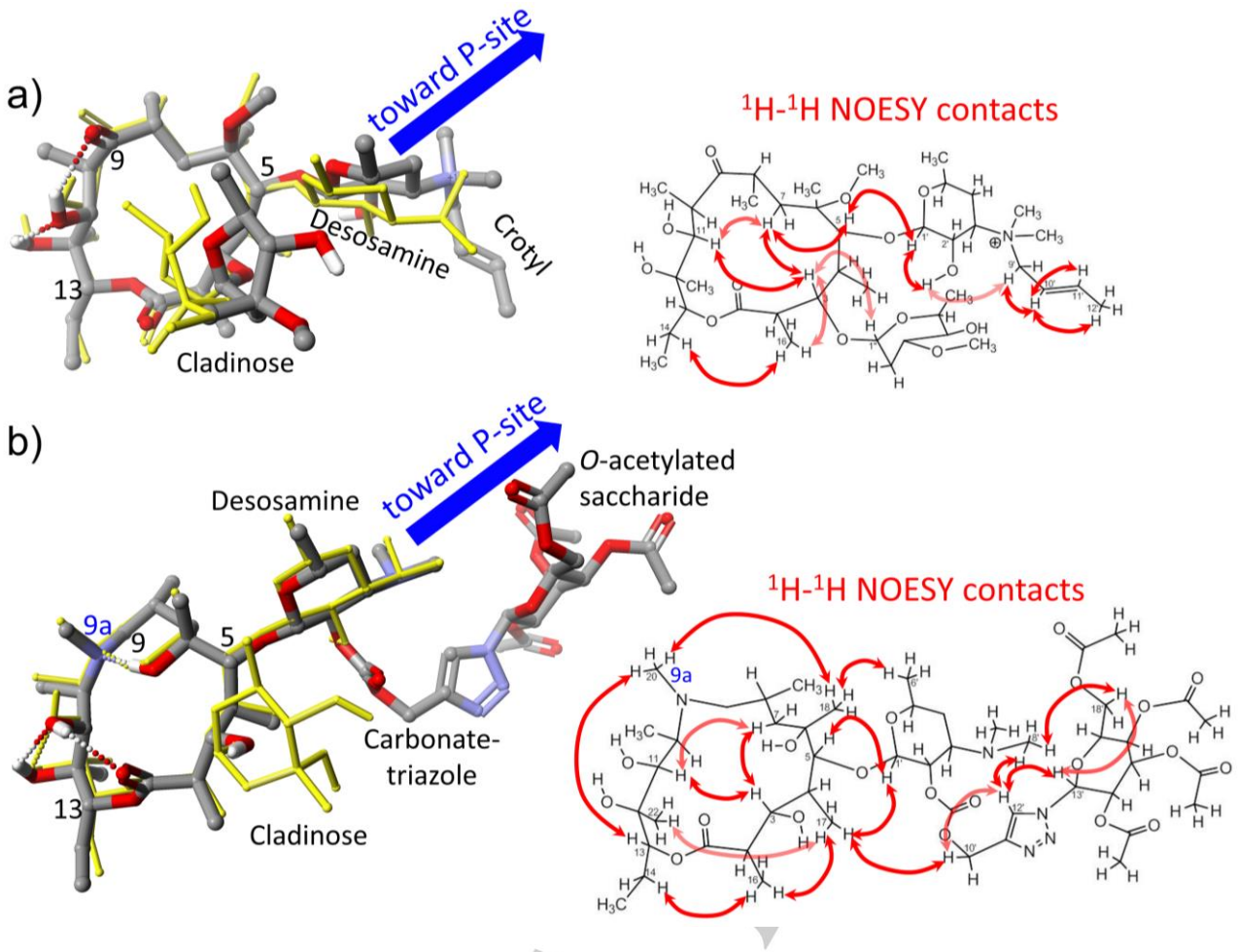


Figure 5. Energetically the most favorable structures of: a) *N*-alkylammonium salt of **CLA** (**4b,** gray) overlapped with that of **CLA** extracted from crystal structure with ribosomes (yellow - PDB 1J5A) [34]; and b) carbonate-triazole derivative of **AZM** (**5x$_{14}$,** gray) superimposed with structure of **AZM** extracted from crystal structure with ribosomes (yellow - PDB 1YHQ) [35]; determined on the basis of ^{1}H-^{1}H NOESY contacts in DMSO-d_6 and in $CDCl_3$ as well as visualized on the basis of DFT theoretical calculations (B88 LYP /GGA/ DFT) [36].

All synthesized derivatives were characterized in details by HPLC, spectroscopic (^{1}H, ^{13}C NMR, FT-IR) and spectrometric (ESI MS) methods (see **Supporting Information, Tables 1S-12S**) as well as by experimentally determined or calculated physico-chemical parameters such as lipophilicity (*c*logP) and water solubility (S_{H2O}) (**Tables 1**).

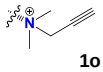
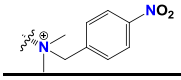
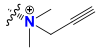
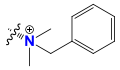
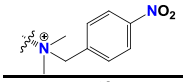
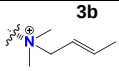
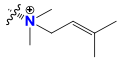
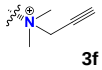
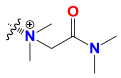
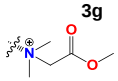
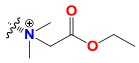
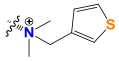
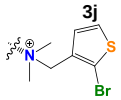
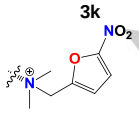
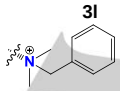
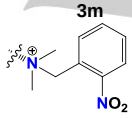
Comparison of physico-chemical and biological data as well as binding of macrolide derivatives to ribosomes

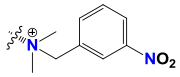
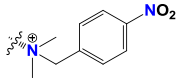
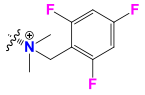
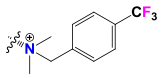
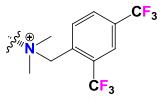
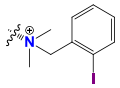
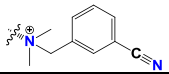
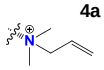
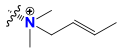
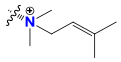
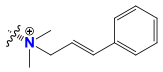
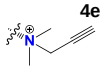
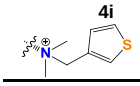
New N-alkylammonium salts of AZM (**1e**, **1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e**-**3u**) and **CLA** (**4a**-**4e**, **4i**) were tested against a number of Gram-positive bacteria, including Staphylococcus aureus strains (ATCC 6538, MRSA-methicillin resistant and MLSB –resistant to macrolides, lincosamides, and streptogramin group B), Staphylococcus epidermidis (ATCC 12228 and ATCC 49134), Enterococcus faecalis (ATCC 29212) and Streptococcus pneumoniae (ATCC 49619 and ATCC 700677, clinical, clinical-mucous), Streptococcus pyogenes (ATCC 19615, clinical) and Streptococcus mitis/oralis (clinical) strains (**Table 1**, **Table 13S** in **Supporting Information**), in the MIC concentration range from 64 to 0.03 μg/mL. Antibacterial data of new macrolides salts of **CLA** and **AZM** were compared to those of reference antibiotics such as: erythromycin (**ERY**), clarithromycin (**CLA**) and azithromycin (**AZM**).

Analysis of the biological data of **CLA** and **AZM** salts indicates that introduction of substituents at the nitrogen is much more beneficial for the biological potency of the 14-membered **CLA** analogs (**4b**, **4c**, **4e**, **4i**) as compared to the 15-membered **AZM** derivatives (**3b**, **3c**, **3e**, **3i**). For *N*-alkylammonium bromides the presence of relatively small substituents at the nitrogen of desosamine as: propargyl (**2e**, **3e** or **4e**), allyl (**4a**), crotyl (**4b**) and dimethylallyl (**4c**), irrespectively of the lactone aglycone size, contributes to unfavourable lipophilicity parameters (clogP = -1.94 - 0.6, **Table 1**) and to the excellent water solubility (S_{H2O} = 4.42-41.2 mg/mL, **Table 1**). Comparison of *c*logP and water solubility parameters for salts **3c** and **4c** showed that the more antibacterially active **4c** exhibits a comparable unfavourable *c*logP and a 4-fold lower water solubility relative to those of **3c**, however still better than **CLA** and **AZM**. Overall, modifications of **CLA** and **AZM** at desosamine nitrogen improve water solubility (S_{H2O} > 2mg/mL) at the expense of decreased lipophilicity (clogP ~ 0), relative to those of reference antibiotics (S_{H2O} **AZM** and **CLA** ~0.3 mg/mL; *c*logP ~2.8). Furthermore, taking into account the physico-chemical parameters (**Table 1**) between the analogs containing cladinose (**2e**, **2l**, **2o;** *c*logP = -0.5, 0.5, -1.9) and non-possessing cladinose (**3e**, **3l**, **3o;** *c*logP 0.3, 0.3, -1) it is shown that the presence of this saccharide within structures of salts slightly enhances their lipophilicity. Comparison of the

biological data for *N*-alkylammonium salts of the lactone macrolides containing both cladinose and acetyl at 2' (**1e**, **1o**) with those having only cladinose (**3b**, **3c**, **3e**-**3u**) and with those lacking cladinose and the acetyl (**2e**, **2l**, **2o**) shows that the lack of the cladinose and presence of the acetyl at 2' are detrimental for antibacterial potency (MICs >64 μg/mL, **Table 1**). The biological tests also showed that our analogs, similarly to **CLA** and **AZM** do not possess a significant potency against MRSA and MSLB *S. aureus* strains (**Table 13S**).

Table 1. MIC values [μg/mL] of Erythromycin (**ERY**), Clarithromycin (**CLA**), Azithromycin (**AZM**) and *N*-alkylammonium salts of **AZM** and **CLA** (**1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e-3u**, **4a-4e**, **4i**), evaluated in the 0.03-64 μg/mL concentration range, together with experimentally determined water solubility (S_{H2O}) and experimentally determined lipophilicity ($clogP_{exp}$) and calculated lipophilicity ($clogP_{calculated}$).

	MIC μg/mL (*Minimal Inhibitory Concentration*)										
	S. pneumoniae				*S. pyogenes*		*S. mitis/ oralis*	*E. faecalis*	Solubility S_{H2O}	Lipophilicity	
compounds	ATCC 49619	ATCC 700677	clinical	clinical-mucous	ATCC 19615	clinical	clinical	ATCC 29212	[mg/mL]	[$clogP_{exp}$]	[$clogP_{calculated}$][a]
ERY	0.125	8	0.5	>64	0.0625	0.0625	0.125	8	0.525	---	2.28
CLA	0.125	2	0.5	>64	0.03125	0.0625	0.03125	4	<0.310	---	2.90
AZM	0.25	16	0.5	>64	0.125	0.125	0.125	32	0.363	---	2.73
1e 	>64	>64	---	---	>64	---	---	>64	---	---	-0.39
1o 	>64	>64	---	---	>64	---	---	>64	---	---	1.01
2e 	>64	>64	---	---	>64	---	---	>64	41.20	-0.30	-1.94
2l 	>64	>64	---	---	>64	---	---	>64	---	---	-0.50
2o 	>64	>64	---	---	>64	---	---	>64	---	---	-0.54
3b 	4	>64	32	>64	4	32	>64	>64	18.05	-0.69	-0.36
3c 	8	>64	32	>64	16	>64	>64	>64	17.21	-0.03	0.42
3e 	4	>64	---	---	2	---	---	>64	35.31	-1.83	-1.09
3f 	64	>64	>64	>64	>64	>64	>64	>64	---	---	-2.34
3g 	>64	>64	>64	>64	>64	>64	>64	>64	---	---	-1.39
3h 	>64	>64	>64	>64	>64	>64	>64	>64	---	---	-1.39
3i 	>64	>64	64	>64	>64	>64	>64	>64	16.54	-0.44	-0.07
3j 	>64	>64	64	>64	>64	>64	>64	>64	---	---	0.86
3k 	16	>64	16	>64	8	16	16	>64	---	---	-0.32
3l 	>64	>64	---	---	>64	---	---	>64	16.71	0.06	0.34
3m 	32	>64	>64	>64	32	16	32	>64	---	---	0.25

compounds	MIC µg/mL (*Minimal Inhibitory Concentration*)								Solubility S_{H2O} [mg/mL]	Lipophilicity	
	S. pneumoniae				*S. pyogenes*		*S. mitis/ oralis*	*E. faecalis*			
	ATCC 49619	ATCC 700677	clinical	clinical-mucous	ATCC 19615	clinical	clinical	ATCC 29212		[*c*logP$_{exp}$]	[clogP$_{calculated}$][a]
ERY	0.125	8	0.5	>64	0.0625	0.0625	0.125	8	0.525	---	2.28
CLA	0.125	2	0.5	>64	0.03125	0.0625	0.03125	4	<0.310	---	2.90
AZM	0.25	16	0.5	>64	0.125	0.125	0.125	32	0.363	---	2.73
3n 	>64	>64	>64	>64	>64	>64	>64	>64	---	---	0.28
3o 	32	>64	---	---	4	---	---	>64	---	---	0.30
3p 	64	>64	64	>64	32	>64	32	>64	---	---	0.69
3r 	64	>64	64	>64	64	>64	64	>64	3.05	0.15	1.24
3s 	4	64	>64	>64	2	2	16	>64	2.16	-0.04	2.06
3t 	64	>64	64	>64	64	>64	64	>64	---	---	1.38
3u 	>64	>64	32	>64	>64	32	>64	>64	---	---	0.07
4a 	2	16	2	>64	0.5	16	16	32	8.33	---	-0.43
4b 	1	>64	0.5	>64	0.5	1	1	>64	4.42	-0.56	-0.18
4c 	2	>64	1	>64	1	2	2	>64	4.36	-0.17	0.60
4d 	8	32	8	>64	4	32	32	>64	3.61	---	1.27
4e 	0.5	64	>64	>64	1	0.25	8	>64	10.87	-1.19	-0.92
4i 	8	>64	4	>64	4	8	4	>64	2.82	-0.20	0.10

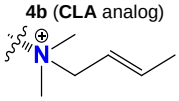
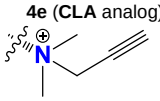
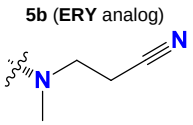
SD_{MIC} = 0

[a] *Molinspiration* - https://www.molinspiration.com/

Data collected in **Table 1** show that the most antibacterially active *N*-alkylammonium salts of all studied are those having 14-membered **CLA** aglycones. The structure-activity relationship analysis among *N*-alkylammonium **CLA** bromides indicates that the best activities were observed for those having unsaturated and relatively small substituents at the desosamine nitrogen (shorter and less bulky - analogs **4a**, **4b**, **4c** and **4e**). Biological activities of **4a**-**4c** and **4d** salts, are comparable or slightly lower with those of **AZM** and **CLA**. It should be noted that at best cases i.e. for **4b** and for **4e** MICs are equal 0.25 or 0.5 µg/mL against *S. pneumoniae* ATCC 49619 and clinical strains as well as *S. pyogenes* ATCC 19615 and *S. pyogenes* clinical strains (**Table 1**). The most beneficial MIC value was obtained for the **4e** derivative containing propargyl against *S. pyogenes* clinical strain (MICs = 0.25 µg/mL). Despite the antibacterial potency of **4e** is good, it is 4-fold lower than that of **CLA**. In turn, compound **4b** shows equal potency as compared to those of **ERY**, **CLA** and **AZM** against *S. pneumoniae* clinical strain at MIC = 0.5 µg/mL, despite its less favourable lipophilicity (*c*logP) and markedly higher water solubility (**Table 1**). Taking into account the only unfavourable lipophilicity clogP and favourable water solubility of our lead compounds **4e** (clogP = - 1.19; S_{H2O} = 10.87) and **4b** (clogP = - 0.56; S_{H2O} = 4.42), similar to the other synthesized derivatives of this-type, their best antibacterial activities among all studied salts are difficult to explain.

Earlier studies reported that **ERY**, **CLA** and **AZM** complexed with various ribosomes of Gram-positive and Gram-negative bacteria, irrespectively of the type of ribosome, are characterized by a relatively low K_d values (10^{-9}-10^{-10} M) indicating their efficient binding to the target (**Table 2**). The K_d values given in **Table 2** show that ribosomes are targets for our lead compounds and that the binding strength is comparable or slightly better as compared to **ERY**, and slightly less favourable in comparison to those of **CLA** or **AZM** antibiotics. It should be also mentioned that our salts **4e** and **4b** possess more beneficial K_d values than studied earlier non-charged **5a** and **5b** analogs of **ERY** (**Table 2**), indicating a positive effect of quaternization of the desosamine nitrogen on formation complex with bacterial ribosomes.

Table 2. Comparison between K_d values of our the most potent quaternary *N*-alkylammonium **CLA** salts (**4b**, **4e**) and the earlier reported ones for **ERY, CLA** and **AZM** as well as selected secondary amine analogs of **ERY** (**5a** and **5b**), modified at the nitrogen of desosamine.

Compound	Ribosomes from bacteria strain:	K_d [M]
ERY	*M. avium*	1.6×10^{-9} [41]
ERY	*E. coli*	1.0×10^{-8} [42]
CLA	*M. smegmatis*	3.5×10^{-10} [41]
CLA	*M. avium*	4.6×10^{-10} [41]
AZM	*B. subtilis*	1.6×10^{-9} [43]
AZM	*E. coli*	2.8×10^{-10} [43]
4b (**CLA** analog) 	*E. coli*	2.73×10^{-8}
4e (**CLA** analog) 	*E. coli*	1.42×10^{-9}
5a (**ERY** analog) 	*E. coli*	1.97×10^{-7} [44]
5b (**ERY** analog) 	*E. coli*	2.14×10^{-7} [44]

Thus, apart from the physico-chemical parameters, other crucial factor such as the binding mode of new macrolide derivatives to their molecular target is here important (**Figure 6**). Our docking studies of different *N*-alkylammonium salts of **CLA** in ribosomal tunnel reveal that newly attached substituent at the nitrogen of desosamine is placed close to the "tunnel guardian" G2484 in bacterial ribosomes (orange, site S1*, **Figures 6a-c**), taking part in the π-π stacking interactions with this nucleotide. Binding energies in ribosomal tunnel ($\Delta H_f°$), calculated for: **4e** ($\Delta H_f°$ = -41.18 kcal/mol; **Figure 6a**) > **4a** ($\Delta H_f°$ = -37.75 kcal/mol – structure not shown) > **4b** ($\Delta H_f°$ = -35.12 kcal/mol; **Figure 6b**) >> **4d** ($\Delta H_f°$ = -23.97 kcal/mol; **Figure 6c**) suggest that the highest energetic profit appear for docking of **CLA** salts containing smaller substituents (**4a**, **4b** and **4e**). Docking studies also showed that *sp* hybridization within the introduced substituent at the nitrogen of desosamine is slightly more energetically favourable than the sp^2 one due to the more efficient interactions with G2484. Thus, analysis of interactions for these **CLA** salts at ribosomal tunnel point on the length and bulkiness of the *N*-substituent as important factors for effective binding to the ribosomal tunnel walls. As shown in **Figure 6**, alkyne (**4e, Figure 6a**) and crotyl (**4b, Figure 6b**) substituents form structures that favour effective π-π stacking with G2484 without any additional conformational changes, whereas the presence of more bulky (*E*)-1-(3-prop-1-enyl)benzene group of **4d** (**Figure 6c**) implicates conformational change within G2484 nucleotide in aim to take part in effective interactions. This result is in line with the antibacterial test results, where *N*-alkylammonium analogs of **CLA** with less bulky and unsaturated ends of the desosamine arm such as: allyl (**4a**), crotyl (**4b**), dimethylallyl (**4c**) and alkyne (**4e**) are much more active against *S. pneumoniae* ATCC 49619 (MICs 0.5-2 μg/mL) and *S. pyogenes* clinical (MICs 0.25-16 μg/mL) strains than those with a more bulky and/or longer substituents as **4d** and **4i** (MICs $_{S.pneumoniae\ ATCC49619}$ = 8 μg/mL and MICs $_{S.pyogenes\ clinical}$ = 8-32 μg/mL) (**Table 1**). It is also interesting that among this group of analogs, exclusively salt **4a** exhibited low and equal potency to that of **AZM** against *E. faecalis* ATCC 29212 strain (MIC 32 μg/mL).

The most potent **AZM** salt **3s** reveals potency in the range MIC = 2-64 μg/mL against *S. pneumoniae*, *S. pyogenes* and *S. mitis/oralis* strains. However, this activity is at least 4-fold lower than those of the standards **ERY**, **CLA** and **AZM**, at the best case (**Table 1**). The question here is why the presence of the less bulky substituents at the nitrogen of desosamine does not contribute to as good antibacterial potency of **AZM** salts as that of **CLA** ones. Comparing of physico-chemical parameters (clogP and S_{H2O}, **Table 1**) between **4b**, **4c** and **3b, 3c** indicates that **AZM** salts have 4-fold better water solubility (S_{H2O}) and a slightly lower lipophilicity (clogP) relative to those of **CLA** salts. First of all, lower activities of **3b** and **3c** in comparison with those of **4b** and **4c** can be explained by energetically less effective binding mode of **AZM** analogs to ribosomal tunnel than derivatives of **CLA**. In view of the earlier models revealing different aglycone orientations between 14-membered **CLA** and 15-membered **AZM** in the ribosomal tunnel[18,34,37], different docking modes of a newly introduced *N*-substituents of **CLA** and **AZM** salts to ribosomes are also expected. In literature it is reported that the 15-membered lactone aglycone ring of **AZM** is oriented parallel, whereas 14-membered aglycone ring of **CLA** is oriented perpendicular relative to the lumen of the ribosomal tunnel. This difference implicates the two alternative binding modes of introduced substituent at the nitrogen of desosamine for **AZM** salts (docking at S1* site - near G2540 or at S2* site - adenylates stack A2099/A2100/A2538, **Figure 7**). As calculated, the binding energy profit of **3s** – site S2* ($\Delta H_f°$ = -18.64 kcal/mol; **Figure 7c**) > **3b** – site S2* ($\Delta H_f°$ = -17.22 kcal/mol; **Figure 7b**) > **3b** – site S1* ($\Delta H_f°$ = -15.21 kcal/mol; **Figure 7a**) > **3s** – site S1* ($\Delta H_f°$ = -6.94 kcal/mol). The theoretical studies indicate that docking of small substituent at the S1* and S2* sites for **3b** is energetically nearly equivalent, whereas the docking of larger and bulky substituent for **3s** can be realized exclusively into the S2* site. The energetic profit of binding **3s** into the site S2* is slightly higher than that of binding of **3b** into the site S2*, which is in agreement with the observed antibacterial activities both of

them. Furthermore, the energetic profit ($\Delta H_f°$ values) of binding **AZM** salts to ribosomes (e.g. for **3b**) is markedly lower than that calculated for **CLA** salts (e.g. for **4b**), what is also in line with the lower potency of **AZM** salts relative to that of **CLA** ones. However, carbonate-triazole analogs of **AZM** (**5x$_1$**-**5x$_{18}$**) do not show any antibacterial activity (MICs >64 μg/mL) revealing that expansion of the desosamine arm by extremely bulky substituents do not influence reorientation of the lactone aglycone of **AZM** derivative with the aim to better fit the arm toward P-site of the ribosomal tunnel. This result for **AZM** derivatives also confirms the importance of the availability of a "free" hydroxyl group at desosamine for effective intermolecular H-bonding of the macrolide with the nitrogen of nucleotides A2099 (*H. marismortui*)/A2041(*D. radiodurans*) of the ribosomal tunnel.

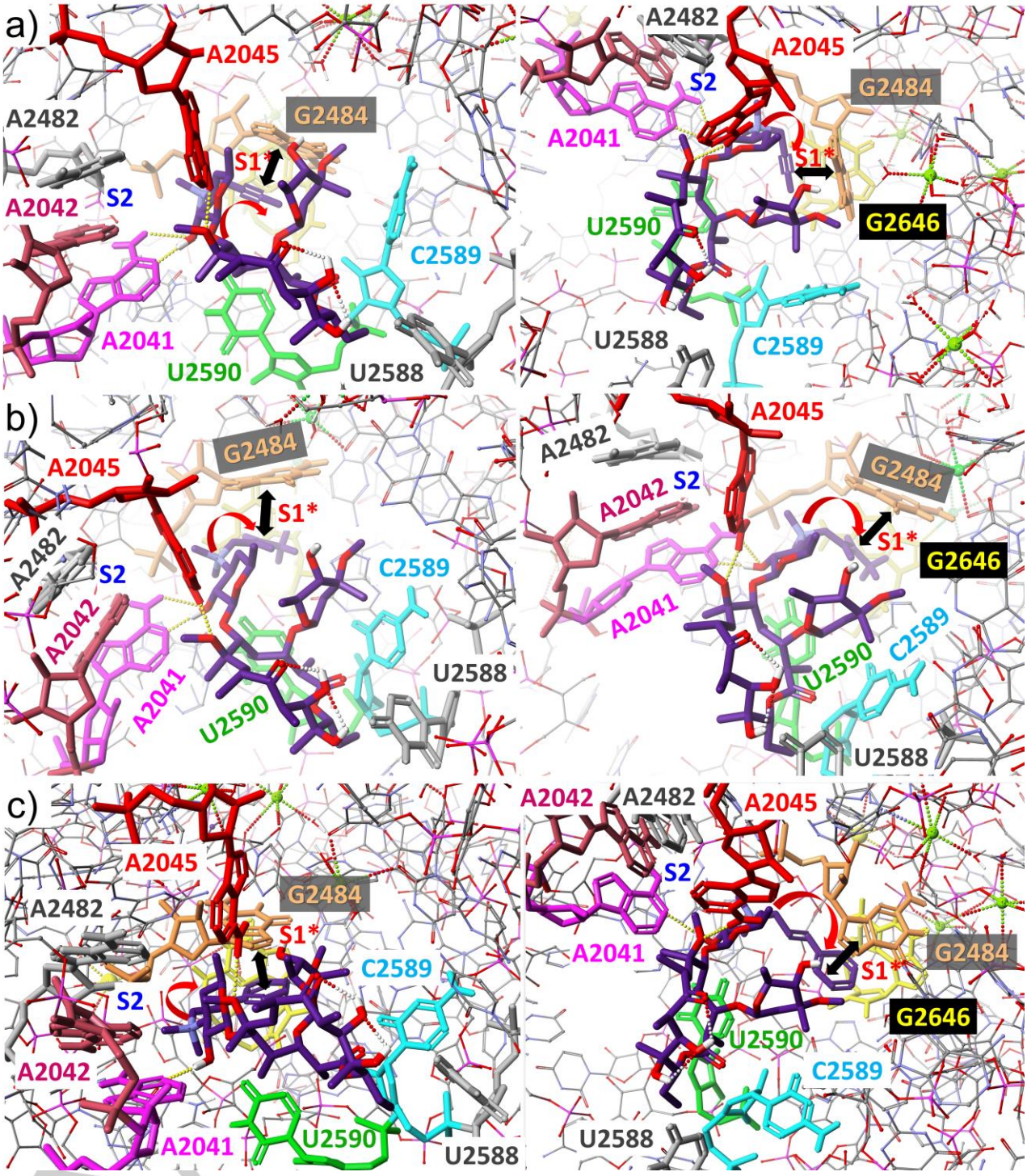


Figure 6. Binding modes of *N*-alkylammonium salts of **CLA** in ribosomal tunnel of *D. radiodurans* (left panel - projection from A2045 side; right panel - projection from the U2588 side): a) **4e**, b) **4b** and c) **4d**. Models were built from atom coordinates extracted from X-ray structures of **CLA**-ribosome complex (PDB 1J5A) [34], and *via* optimization of the antibiotic - ribosomal tunnel interactions (cutted cube of 50Å×50Å×50Å dimensions) using MM3 and MOG-PM6 method of *Scigress* package [36]. Intermolecular interactions between salts (violet) and ribosomes are marked by pale yellow dots; S1* and S2 are an alternative binding sites considered.

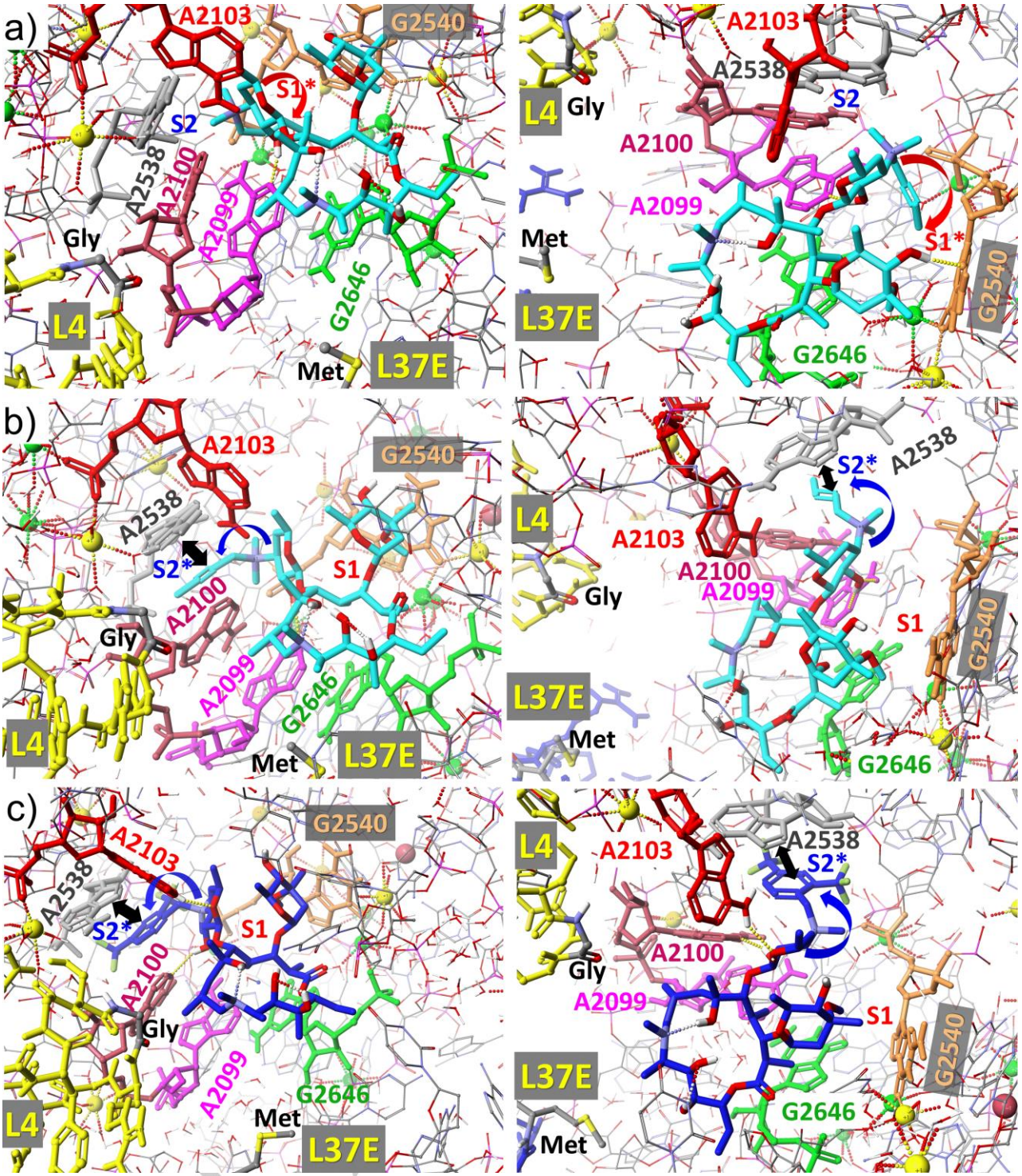


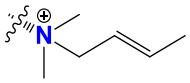
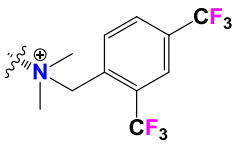
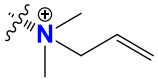
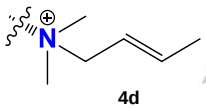
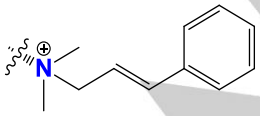
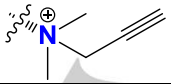
Figure 7. Binding modes of *N*-alkylammonium salts of **AZM** in ribosomal tunnel of *H. marismortui* (left panel - projection from A2103 side; right panel - projection from the opposite side relative to the adenylates stack A2099/A2100/A2538): a) **3b** docked at S1* site, b) **3b** docked at S2* site and c) **3s** docked at S2* site. Models were built from atom coordinates extracted from X-ray structures of **AZM**-ribosome complex (PDB 1YHQ) [35], and *via* optimization of the antibiotic - ribosomal tunnel interactions (cutted cube of 50Å×50Å×50Å dimensions) using MM3 and MOG-PM6 method of *Scigress* package [36]. Intermolecular interactions between salts (pale blue/dark blue) and ribosomes are marked by pale yellow dots; S1* and S2* are an alternative binding sites considered.

Cytotoxic effect of the most active CLA and AZM salts in normal cell line

Results of cytotoxicity studies of **AZM** and **CLA** salts, performed in Human Dermal Fibroblasts cell line (HDF), were collected in **Table 3**. Irrespectively, whether the salt is built on the basis of 14-membered (**4a**, **4b**, **4d**, **4e**) or on 15-membered lactone scaffolds (**3b**, **3s**), it shows lower cytotoxicity in comparison with those of reference antibiotics **ERY**, **CLA** and **AZM**. The most antibacterially potent derivatives **4e** and **4b** show about 3-fold lower cytotoxicity in normal cell line (IC_{50} ~ 70 μM) when

compared to the cytotoxicity of **CLA** (IC_{50} ~ 20 μM). Similar cytotoxicity as for **4e** and **4b** is exhibited also by the allyl derivative of **CLA** (**4a,** IC_{50} = 73.43 μM) whereas less antibacterial active **4d** reveals at the same time the lowest cytotoxicity among the studied **CLA** salts (IC_{50} = 98.14 μM). As it was described above, the **AZM** salts (e.g. **3b**) shown to be less antibacterially active than the corresponding **CLA** ones (e.g. **4b**). This result is in line with the lower cytotoxicity of **AZM** salts than those based on **CLA** scaffold. It can be also mentioned that the cytotoxicity of **AZM** salts **3b** and **3s** is 6-fold and 8-fold lower than the standard antibiotic **AZM**, respectively. These data taken together with the result of antibacterial tests demonstrate that quaternization of the desosamine nitrogen with a short, less bulky and unsaturated substituents within **CLA** framework is related not only to good antibacterial effect against tested *S. pneumoniae* and *S. pyogenes* strains but also resulted in significantly decreased cytotoxicity in HDF cell line, when compared to those of reference antibiotics.

Table 3. IC_{50} values for Erythromycin (**ERY**), Clarithromycin (**CLA**), Azithromycin (**AZM**) and selected, the most antibacterially potent *N*-alkylammonium salts of **AZM** and **CLA**, determined in Human Dermal Fibroblast cell line (HDF), given in μM concentration (± SD).

HDF (Human Dermal Fibroblasts)	
Compound	Cytotoxicity IC_{50} [μM]
ERY	26.19±0.21
CLA	20.02±0.34
AZM	21.94±0.52
3b 	121.69±0.98
3s 	171.11±1.02
4a 	73.43±0.54
4b 	72.03±1.37
4d 	98.14±0.92
4e 	67.11±0.75

Conclusion

Eighteen new carbonate-triazole derivatives of **AZM** and twenty nine new *N*-alkylammonium bromides of **AZM** and **CLA** were synthesized *via* transformations including quaternization of the desosamine nitrogen (S_N2) or nucleophilic substitution at carbonyl/Huisgen dipolar cycloadditions of CuAAC type reactions. Unexpected follow-up cyclization reactions of *N*-alkylammonium bromides of **AZM** containing end-ester group resulted in the loss of antibacterial potency. The most active *N*-alkylammonium bromides of **CLA** toward *S. pneumoniae* strains (ATTC 49619, clinical) and *S. pyogenes* (ATCC 19615, clinical) were those with relatively short and less bulky unsaturated substituent such as: allyl, alkyne, crotyl, dimethylallyl, attached at the nitrogen of desosamine (MICs in the range of 0.25-16 μg/mL). Our lead compounds **4b** and **4e** revealed good antibacterial activity against *S. pneumoniae* and *S. pyogenes* strains (MICs 0.5 or 0.25 μg/mL) at 3-fold lower cytotoxicity assessed in HDF cell line, when compared to reference antibiotics **ERY**, **CLA** and **AZM**. The observed SAR among **CLA** salts seems to be less dependent on physico-chemical properties (clogP, S_{H2O}) than on the binding mode at ribosomal tunnel – site near A2103 (*H. marismortui*)/A2045 (*D. radiodurans*). Docking studies performed in the ribosomal tunnel showed that the presence of relatively short, less bulky and unsaturated substituents attached to the quaternized nitrogen of the desosamine, which enable stabilizing π-π stacking interaction with G2540(*H. marismortui*)/G2484(*D. radiodurans*), is a one of reasons of **4b** and **4e** higher antibacterial potency comparing to the other derivatives, having longer and a more bulky unsaturated substituents.

Experimental Section

General procedures

All reagents and all solvents were obtained from Sigma-Aldrich, Carbosynth and Abcr. All manipulations were carried out under nitrogen atmosphere in dried glassware. Reactions mixtures were monitored by High-Performance Liquid Chromatography. HPLC separations were performed with a Dionex Ultimate 3000 equipped with LPG-3400 SD gradient pump using Thermo GOLD C18 150×4.6 mm (5 μm) Accucore XL column, TCC-3000SD thermostat to columns (column temp. equal 25 ºC) and Dionex VWD-3400RS variable wavelength UV-vis detector. The flow rate was 1 mL/min with injection volumes of 10 μL. Depending on the sample a different mobile phase was used, detail information are given after *R*t in the bracket. A 0.1 M solution of ammonium acetate in a water:acetonitryl (1:1) mixture was used as a buffer. The analytical wavelength was λ_{max}=220 nm.

The FT-IR spectra of **1e**, **1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e-3u**, **4a-4e**, **4i**, **5x$_1$-5x$_{17}$** derivatives as powders were recorded in KBr pellet (1.8 mg/200 mg). All FT-IR spectra were recorded with an IFS 113v FT-IR spectrophotometer (Bruker, Karlsruhe) equipped with a DTGS detector; resolution 2 cm^{-1}, NSS = 125, range 4000-400 cm^{-1}. The Happ-Genzel apodization function was used.

The ^1H and ^{13}C NMR measurements of **1e**, **1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e-3u**, **4a-4e**, **4i** analogs were performed in DMSO-d_6 and **5x$_1$-5x$_{18}$** analogs were performed in $CDCl_3$ on Bruker Avance III 600 MHz, Bruker Avance III 500 MHz, Agilent VNMRS 400 MHz spectrometers. For Bruker Avance 600 MHz spectrometer: the operating frequencies for ^1H measurements was 600.08 MHz; pulse width corresponding to the flip angle of 45^0;

spectral width swh = 9842.5 Hz; acquisition time at= 0.2 sec; relaxation delay d_1=1.0 s; T = 293.0 K, TMS was used as the internal standard. No window function or zero filling were used. Digital resolution was 0.2 Hz/point. ^{13}C NMR spectra were recorded at the operating frequency 150.454 MHz; pulse width corresponding to the flip angle of 60^0; sw = 19000 Hz; at = 1.8 s; d_1=1.0 s; T = 293.0 K and TMS as the internal standard. Line broadening parameters of 0.5 or 1 Hz were applied. For Bruker Avance 500 MHz spectrometer: the operating frequencies for ^{1}H measurements was 500.25 MHz; pulse width corresponding to the flip angle of 45^0; spectral width swh = 11029.4 Hz; acquisition time at= 0.2 sec; relaxation delay d_1=1.0 s; T = 257.0 K, TMS was used as the internal standard. No window function or zero filling were used. Digital resolution was 0.2 Hz/point. ^{13}C NMR spectra were recorded at the operating frequency 125.79 MHz; pulse width corresponding to the flip angle of 60^0; sw = 35714.3 Hz; at = 2.0 s; d_1=0.92 s; T = 257.0 K and TMS as the internal standard. Line broadening parameters of 0.5 or 1 Hz were applied. For Agilent VNMRS 400 MHz spectrometer: the operating frequencies for ^{1}H measurements was 402.65 MHz; pulse width corresponding to the flip angle of 45^0; spectral width swh = 8064.5 Hz; acquisition time at= 5 sec; relaxation delay d_1=1.0 s; T = 293.0 K, TMS was used as the internal standard. No window function or zero filling were used. Digital resolution was 0.2 Hz/point. ^{13}C NMR spectra were recorded at the operating frequency 101.26 MHz; pulse width corresponding to the flip angle of 60^0; sw = 26041.7 Hz; at = 1.3 s; d_1=1.0 s; T = 293.0 K and TMS as the internal standard. Line broadening parameters of 0.5 or 1 Hz were applied. The ^{1}H and ^{13}C NMR resonances in solution were unambiguously assigned on the basis of the ^{1}H -^{1}H NOESY, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC and ^{1}H-^{13}C HSQC correlation spectra.

Syntheses

General procedure for the synthesis of new *N*-alkylammonium 2'-*O*-acetyl azithromycin bromide derivatives 1e, 1o together with the analytical data.

Azithromycin (**AZM**) was purchased from Carbosynth (>98%). **AZM** (100.0 mg, 0.13 mmol) was dissolved in 5 ml ACN and catalytic quantity of acetic anhydride was added. The mixture was stirred at 25°C for 24 hours and after that the solvent was evaporated to dryness, dissolved in 50 ml of EtOAc and extracted twice with 50 ml of saturated $NaHCO_3$. The separated organic layers were evaporated. Next, the obtained solid state product was dissolved in 5 ml anhydrous ACN, respective mixtures were prepared with each of following compounds taken separately (0.52 mmol): propargyl bromide and 4-nitrobenzyl bromide. The mixtures were stirred at room temperature for 5 hours. Next, the reaction mixture was evaporated to dryness, dissolved in 2 ml CH_2Cl_2 and the obtained solution was added by dropwise into the 50 ml hexane. Obtained precipitate was filtered and dried under the vacuum. All ^{1}H and ^{13}C NMR data of **1e** and **1o** are collected in **Tables 1S - 2S**.

1e Yield: 78%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.72 (s, 1H), 5.02 (dd, ^3J=10.1 Hz, 6.8 Hz, 1H), 4.87 (d, ^3J=4.8 Hz, 1H), 4.78 (dd, ^3J=10.1 Hz, 2.8 Hz, 1H), 4.60 (d, ^3J=6.8 Hz, 1H), 4.48 (dd, ^2J=16.6 Hz, ^4J=2.5 Hz, 1H), 4.36 (d, ^3J=7.3 Hz, 1H), 4.30 (s, 1H), 4.28 (d, ^3J=9.0 Hz,1H), 4.26 (dd, ^2J=16.0 Hz, ^4J=2.5 Hz, 1H), 4.18 (t, ^4J=2.4 Hz, 1H), 4.10 (d, ^3J=4.7 Hz, 1H), 4.02 (m, 1H), 3.97 (m, 1H), 3.88 (m, 1H), 3.51 (d, ^3J=6.1 Hz, 1H), 3.41 (d, ^3J=8.1 Hz, 1H), 3.27 (s, 3H), 3.11 (s, 3H), 3.08 (s, 3H), 2.95 (dd, ^3J=9.5 Hz, 7.2 Hz, 1H), 2.69 (m, 1H), 2.65 (m, 1H), 2.36 (d, ^2J=11.5 Hz, 1H), 2.27 (d, ^2J=15.0 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H), 2.10 (m, 2H), 1.92 (m, 1H), 1.88 (m, 1H), 1.79 (m, 1H), 1.79 (d, ^3J=12.4 Hz, 1H), 1.54 (dd, ^2J=15.0 Hz, ^3J=5.0 Hz, 1H), 1.39 (d, ^2J=14.3 Hz, 1H), 1.35 (m, 1H), 1.22 (m, 1H), 1.19 (d, ^3J=5.9 Hz, 1H), 1.16 (s, 3H), 1.16 (d, ^3J=6.7 Hz, 3H), 1.14 (s, 3H), 1.10 (d, ^3J=7.5 Hz, 3H), 1.00 (s, 3H), 0.93 (d, ^3J=6.7 Hz, 3H), 0.82 (d, ^3J=6.9 Hz, 3H), 0.79 (t, ^3J=7.4 Hz, 3H), 0.79 (d, ^3J=7.6 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 176.9, 169.0, 98.8, 94.4, 83.9, 83.0, 77.1, 77.0, 76.4, 75.0, 73.6, 73.0, 72.3, 72.1, 70.1, 68.6, 68.4, 65.9, 64.9, 61.4, 55.9, 50.0, 49.1, 49.0, 44.5, 44.1, 44.0, 35.7, 34.5, 32.0, 27.4, 25.9, 22.0, 21.6, 21.1, 20.9, 20.9, 18.5, 17.6, 14.7, 10.9, 8.9, 6.7; FT-IR (KBr pellet): a broad band 3405 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν(O_2'-H)+ν(O_4''-H), 2638 cm^{-1} ν(O_6-H), 2126 ν(C≡C), 1752 cm^{-1} ν(C=O)$_{acetyl}$, 1730 cm^{-1} ν(C_1=O)$_{lactone}$, 1212 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 908.4611; Elemental analysis $C_{43}H_{77}BrN_2O_{13}$: calculated: C=56.76%; H=8.53%; Br=8.78%; N=3.08%; measured: C=56.78%; H=8.51%; Br=8.81 %; N=3.06%; HPLC: R_t = 1.98 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 97%;

1o Yield: 80%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.35 (d, ^3J=8.6, 2H), 7.90 (d, ^3J=8.4, 2H), 7.75 (s, 1H), 5.17 (dd, ^3J=9.8 Hz, 6.6 Hz, 1H), 4.85 (d, ^2J=12.6 Hz, 1H), 4.84 (d, ^3J=4.7 Hz, 1H), 4.74 (d, ^3J=10.8 Hz, 1H), 4.60 (d, ^3J=6.2 Hz, 1H), 4.58 (d, ^2J=12.2 Hz, 1H), 4.31 (s, 1H), 4.30 (m, 2H), 4.15 (m, 1H), 4.00 (dq, ^3J=12.2 Hz, 6.2 Hz, 1H), 3.92 (ddd, ^3J=11.8 Hz, 9.7 Hz, 4.5 Hz, 1H), 3.81 (q, ^3J=7.4 Hz, 1H), 3.55 (d, ^3J=6.7 Hz, 1H), 3.42 (d, ^3J=8.7 Hz, 1H), 3.22 (s, 3H), 3.05 (s, 3H), 3.00 (s, 3H), 2.96 (d, ^3J=8.2 Hz, 1H), 2.67 (m, 2H), 2.35 (m, 1H), 2.28 (m, 2H), 2.21 (s, 3H), 2.21 (s, 3H), 2.10 (m, 1H), 1.94 (m, 1H), 1.90 (m, 1H), 1.90 (d, ^3J=11.8 Hz, 1H), 1.77 (m, 1H), 1.54 (dd, ^2J=14.6 Hz, ^3J=4.7 Hz, 1H), 1.42 (d, ^2J=14.9 Hz, 1H), 1.34 (m, 1H), 1.24 (m, 1H), 1.21 (s, 3H), 1.21 (d, ^3J=6.2 Hz, 1H), 1.18 (d, ^3J=6.7 Hz, 3H), 1.14 (s, 3H), 1.11 (d, ^3J=7.1 Hz, 3H), 1.01 (s, 3H), 0.94 (d, ^3J=6.7 Hz, 3H), 0.85 (d, ^3J=7.5 Hz, 3H), 0.82 (d, ^3J=6.0 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.0, 169.1, 148.7, 134.9, 134.9, 134.8, 123.8, 123.8, 98.8, 94.4, 82.7, 77.0, 77.0, 76.4, 75.0, 73.5, 72.9, 72.5, 70.2, 69.7, 68.5, 66.0, 65.0, 64.7, 61.4, 49.6, 49.0, 47.6, 44.6, 41.2, 41.1, 35.7, 34.5, 32.1, 27.5, 26.0, 22.0, 21.7, 20.9, 20.9, 20.9, 18.5, 17.6, 14.8, 10.9, 8.9, 6.7; FT-IR (KBr pellet): a broad band 3406 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν(O_2'-H)+ν(O_4''-H), 2637 cm^{-1} ν(O_6-H), 2126 cm^{-1} ν(C≡C), 1749 cm^{-1} ν(C=O)$_{acetyl}$, 1729 cm^{-1} ν(C_1=O)$_{lactone}$, 1527 cm^{-1} ν(NO_2), 1457 ν(C=C), 1347 cm^{-1} ν(NO_2), 1211 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 1005.4778; Elemental analysis $C_{47}H_{80}BrN_3O_{15}$: calculated: C=56.05%; H=8.01%; Br=7.93%; N=4.17%; measured: C=56.10%; H=8.03%; Br=7.91%; N=4.16%; HPLC: R_t = 1.98 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 95%;

General procedure for the synthesis of new *N*-alkylammonium decladinosyl azithromycin bromide derivatives 2e, 2l, 2o together with the analytical data.

Azithromycin (**AZM**) was purchased from Carbosynth (>98%). **AZM** (100.0 mg, 0.13 mmol) was dissolved in 5 ml acetone and 2 ml 0.25M HCl. The mixture was stirred at 25°C for 24 hours and after that 2 ml saturated $NaHCO_3$ was added to stop the reactions. Organic layer was extracted three time with 50 ml of saturated $NaHCO_3$. The separated organic layers were evaporated. Next, the obtained solid state product was dissolved in 5 ml anhydrous ACN, respective mixtures were prepared with each of following compounds taken separately (0.52 mmol): propargyl bromide, benzyl bromide and 4-nitrobenzyl bromide. The mixtures were stirred at room temperature for 4 hours. Next, the reaction mixture was evaporated to dryness, dissolved in 2ml CH_2Cl_2 and the obtained solution was added by dropwise into the 50 ml hexane. Obtained precipitate was filtered and dried under the vacuum. All ^{1}H and ^{13}C NMR data of **2e**, **2l**, **2o** are collected in **Tables 1S - 2S**.

2e Yield: 88%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 6.32 (s, 1H), 5.73 (d, ^3J=4.8 Hz, 1H), 5.46 (d, ^3J=6.6 Hz, 1H), 4.97 (dd, ^3J=11.1 Hz, 2.3 Hz, 1H), 4.74 (d, ^3J=7.0 Hz, 1H), 4.61 (dd, ^2J=16.3 Hz, ^4J=2.5 Hz, 1H), 4.55 (dd, ^2J=16.1 Hz, ^4J=2.6 Hz, 1H), 4.34 (s, 1H), 4.07 (m, 1H), 4.06 (d, ^3J=8.2 Hz, 1H), 3.70 (m, 1H), 3.55 (m, 2H), 3.46 (d, ^3J=1.8 Hz, 1H), 3.42 (d, ^3J=8.3 Hz, 1H), 3.34 (m, 1H), 3.20 (s, 3H), 3.12 (s, 3H), 2.68 (q, ^3J=6.9 Hz, 1H), 2.51 (m, 1H), 2.31 (dd, ^2J=11.8 Hz, ^3J=3.4 Hz, 1H), 2.23 (s, 3H), 2.15 (q, ^3J=7.6 Hz, 1H), 2.11 (m, 1H), 2.05 (m, 1H), 1.77 (m, 2H), 1.62 (d, ^3J=11.9 Hz, 1H), 1.47 (d, ^2J=14.1 Hz, 1H), 1.40 (dq, ^3J=11.1 Hz, 7.1 Hz, 1H), 1.32 (dd, ^2J=14.6 Hz, ^3J=5.5 Hz, 1H), 1.20 (d, ^3J=6.0 Hz, 1H), 1.12 (s, 3H), 1.11 (d, ^3J=7.1 Hz, 3H), 0.98 (s, 3H), 0.95 (d, ^3J=6.7 Hz, 3H), 0.88 (d, ^3J=7.2 Hz, 3H), 0.84 (d, ^3J=7.0 Hz, 3H), 0.76 (t, ^3J=7.3 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 175.4, 100.7, 87.5, 83.1, 76.7,

76.4, 76.1, 73.6, 72.9, 72.3, 71.1, 70.3, 69.0, 66.6, 61.1, 55.2, 49.3, 49.0, 43.2, 40.7, 36.2, 35.3, 32.4, 26.2, 25.9, 21.4, 20.8, 20.7, 17.8, 16.3, 10.5, 8.4, 6.3; FT-IR (KBr pellet): a broad band 3290 – 3494 cm^{-1} $\nu(O_{11}$-H)+$\nu(O_{12}$-H)+$\nu(O_{2''}$-H)+$\nu(O_{4''}$-H), 2636 cm^{-1} $\nu(O_6$-H), 2132 cm^{-1} ν(C≡C), 1720 cm^{-1} $\nu(C_1{=}O)_{lactone}$, 1466 cm^{-1} δ(C-H), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 708.3565; Elemental analysis $C_{33}H_{61}BrN_2O_9$: calculated: C=55.84%; H=8.66%; Br=11.26%; N=3.95%; measured: C=55.90%; H=8.62%; Br=11.24%; N=3.97%; HPLC: R_t = 1.95 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 94%;

2l Yield: 83%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.60 (dd, ^3J=7.4 Hz, ^4J=1.6 Hz 2H), 7.52 (m, 3H), 6.36 (s, 1H), 5.83 (d, ^3J=3.7 Hz, 1H), 5.48 (d, ^3J=6.6 Hz, 1H), 4.98 (dd, ^3J=11.1 Hz, 2.3 Hz, 1H), 4.79 (d, ^3J=6.9 Hz, 1H), 4.76 (s, 2H), 4.35 (s, 1H), 4.07 (d, ^3J=8.1 Hz, 1H), 3.72 (m, 1H), 3.71 (m, 1H), 3.53 (m, 1H), 3.49 (d, ^3J=1.7 Hz, 1H), 3.43 (d, ^3J=8.3 Hz, 1H), 3.37 (m, 1H), 2.98 (s, 6H), 2.69 (q, ^3J=7.1 Hz, 1H), 2.54 (m, 1H), 2.32 (d, ^2J=12.2 Hz, 1H), 2.24 (s, 3H), 2.18 (d, ^3J=7.7 Hz, 1H), 2.15 (d, ^2J=12.2 Hz, 1H), 2.07 (m, 1H), 1.77 (m, 2H), 1.69 (m, 1H), 1.50 (d, ^2J=14.2 Hz, 1H), 1.41 (m, 1H), 1.35 (dd, ^2J=14.8 Hz, ^3J=5.4 Hz, 1H), 1.22 (d, ^3J=6.1 Hz, 1H), 1.14 (s, 3H), 1.13 (d, ^3J=6.8 Hz, 3H), 1.00 (s, 3H), 0.96 (d, ^3J=6.5 Hz, 3H), 0.94 (d, ^3J=7.3 Hz, 3H), 0.85 (d, ^3J=7.0 Hz, 3H), 0.77 (t, ^3J=7.3 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 175.4, 133.5, 133.5, 130.2, 128.9, 128.9, 128.3, 101.0, 87.8, 76.7, 76.4, 76.1, 73.6, 72.3, 71.7, 70.4, 69.0, 66.8, 66.0, 61.6, 49.4, 48.1, 43.2, 40.8, 36.2, 35.4, 32.2, 26.2, 25.9, 21.4, 20.8, 20.7, 17.8, 16.3, 10.5, 8.5, 6.3; FT-IR (KBr pellet): a broad band 3345 cm^{-1} $\nu(O_{11}$-H)+$\nu(O_{12}$-H)+$\nu(O_{2''}$-H)+$\nu(O_{4''}$-H), 2637 cm^{-1} $\nu(O_6$-H), 1760 cm^{-1} $\nu(C_1{=}O)_{lactone}$, 1457 ν(C=C), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 760.3889; Elemental analysis $C_{37}H_{65}BrN_2O_9$: calculated: C=58.33%; H=8.60%; Br=10.49%; N=3.68%; measured: C=58.31%; H=8.63%; Br=10.52%; N=3.70%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 96%;

2o Yield: 79%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.35 (d, ^3J=8.4 Hz, 2H), 7.91 (d, ^3J=8.4 Hz, 2H), 6.34 (s, 1H), 5.88 (d, ^3J=3.8 Hz, 1H), 5.51 (d, ^3J=6.7 Hz, 1H), 4.99 (dd, ^3J=11.0 Hz, 2.3 Hz, 1H), 4.94 (d, ^2J=12.5 Hz, 1H), 4.88 (d, ^2J=12.4 Hz, 1H), 4.79 (d, ^3J=6.8 Hz, 1H), 4.35 (s, 1H), 4.08 (d, ^3J=8.2 Hz, 1H), 3.72 (m, 2H), 3.53 (m, 1H), 3.49 (m, 1H), 3.44 (d, ^3J=8.3 Hz, 1H), 3.38 (m, 1H), 3.04 (s, 3H), 3.03 (s, 3H), 2.69 (q, ^3J=6.9 Hz, 1H), 2.54 (dq, ^3J=10.4 Hz, 6.6 Hz, 1H), 2.33 (dd, ^2J=12.2 Hz, ^3J=3.4 Hz, 1H), 2.24 (s, 3H), 2.19 (d, ^3J=7.6 Hz, 1H), 2.13 (t, ^2J=12.4 Hz, 1H), 2.11 (d, ^3J=12.6 Hz, 1H), 1.77 (m, 2H), 1.70 (m, 1H), 1.49 (d, ^2J=14.1 Hz, 1H), 1.41 (m, 1H), 1.35 (dd, ^2J=14.9 Hz, ^3J=5.7 Hz, 1H), 1.21 (d, ^3J=6.0 Hz, 1H), 1.14 (s, 3H), 1.14 (d, ^3J=6.2 Hz, 3H), 1.00 (s, 3H), 0.96 (d, ^3J=7.2 Hz, 3H), 0.95 (d, ^3J=8.0 Hz, 3H), 0.84 (d, ^3J=7.0 Hz, 3H), 0.77 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 175.4, 148.5, 135.5, 135.1, 135.1, 123.7, 123.7, 101.0, 88.0, 76.8, 76.4, 76.1, 73.6, 72.3, 72.0, 70.4, 69.0, 66.7, 64.6, 61.6, 49.8, 48.3, 43.3, 40.8, 36.2, 35.4, 32.2, 26.2, 25.9, 21.4, 20.9, 20.7, 17.8, 16.3, 10.5, 8.5, 6.3; FT-IR (KBr pellet): a broad band 3345 cm^{-1} $\nu(O_{11}$-H)+$\nu(O_{12}$-H)+$\nu(O_{2''}$-H)+$\nu(O_{4''}$-H), 2638 cm^{-1} $\nu(O_6$-H), 1712 cm^{-1} $\nu(C_1{=}O)_{lactone}$, 1527 cm^{-1} $\nu(NO_2)$, 1457 ν(C=C), 1347 cm^{-1} $\nu(NO_2)$, 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 805.3731; Elemental analysis $C_{37}H_{64}BrN_3O_{11}$: calculated: C=55.08%; H=8.00%; Br=9.90%; N=5.21%; measured: C=55.06%; H=8.01%; Br=9.89%; N=5.19%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 95%;

General procedure for the synthesis of new *N*-alkylammonium azithromycin bromide derivatives 3b, 3c, 3e-3u together with the analytical data.

Azithromycin (**AZM**) was purchased from Carbosynth (>98%). **AZM** (100.0 mg, 0.13 mmol) was dissolved in 5 ml anhydrous ACN, respective mixtures were prepared with each of following compounds taken separately (0.52 mmol): crotyl bromide, 3,3-dimethylallyl bromide, propargyl bromide, 2-bromo-*N*,*N*-dimethylacetamide, methyl bromoacetate, ethyl bromoacetate, 3-(bromomethyl)thiophene, 3-(bromomethyl)-1-benzothiophene, 2-(bromomethyl)-5-nitrofuran, benzyl bromide, 2-nitrobenzyl bromide, 3-nitrobenzyl bromide, 4-nitrobenzyl bromide, 2,4,6-trifluorobenzyl bromide, 4-(trifluoromethyl)benzyl bromide, 2-iodobenzyl bromide and 3-(bromomethyl)benzonitrile. The mixtures were stirred at room temperature for 2-24 hours. Next, the reaction mixture was evaporated to dryness, dissolved in 2ml CH_2Cl_2 and the obtained solution was added by dropwise into the 50 ml hexane. Obtained precipitate was filtered and dried under the vacuum. All ^{1}H and ^{13}C NMR data of **3b**, **3c**, **3e-3u** are collected in **Tables 1S - 6S**.

3b Yield: 98%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.66 (s, 1H), 6.03 (dq, ^3J=13.4 Hz, 6.6 Hz, 1H), 5.84 (d, ^3J=5.4 Hz, 1H), 5.69 (m, 1H), 4.86 (d, ^3J=4.8 Hz, 1H), 4.76 (dd, ^3J=10.1 Hz, 2.9 Hz, 1H), 4.46 (d, ^3J=7.0 Hz, 1H), 4.31 (s, 1H), 4.30 (m, 1H), 4.30 (d, ^3J=6.0 Hz, 1H), 4.23 (d, ^3J=7.6 Hz, 1H), 4.15 (m, 1H), 4.14 (m, 1H), 4.02 (m, 1H), 3.72 (m, 1H), 3.58 (m, 1H), 3.53 (d, ^3J=6.9 Hz, 1H), 3.44 (d, ^3J=7.6 Hz, 1H), 3.43 (m, 1H), 3.25 (s, 3H), 3.03 (s, 3H), 2.97 (s, 3H), 2.94 (dd, ^3J=9.6 Hz, 7.6 Hz, 1H), 2.67 (m, 2H), 2.38 (m, 1H), 2.27 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.12 (t, ^2J=11.7 Hz, 1H), 2.01(dd, ^3J=10.5 Hz, 3.8 Hz, 1H), 1.93 (m, 1H), 1.91 (m, 1H), 1.75 (m, 1H), 1.78 (m, 1H), 1.77 (d, ^3J=7.9 Hz, 1H), 1.56 (d, ^2J=14.5 Hz, 1H), 1.50 (m, 1H), 1.37 (ddq, ^2J=14.7 Hz, ^3J=10.3 Hz, 7.4 Hz, 1H), 1.27 (m, 1H), 1.17 (s, 3H), 1.17 (d, ^3J=7.0 Hz, 3H), 1.15 (s, 3H), 1.14 (d, ^3J=6.1 Hz, 1H), 1.09 (d, ^3J=7.5 Hz, 3H), 1.01 (s, 3H), 0.95 (d, ^3J=6.2 Hz, 3H), 0.93 (d, ^3J=6.9 Hz, 3H), 0.85 (d, ^3J=6.8 Hz, 3H), 0.79 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 139.5, 119.1, 101.1, 94.4, 83.4, 77.3, 77.1, 76.3, 75.0, 73.6, 72.9, 72.4, 70.6, 69.1, 68.7, 66.6, 65.7, 64.8, 61.5, 49.2, 48.8, 47.7, 44.6, 41.7, 41.6, 35.7, 34.5, 32.2, 27.4, 26.1, 22.1, 21.0, 20.9, 20.9, 18.5, 18.1, 17.7, 14.8, 10.9, 9.2, 6.7; FT-IR (KBr pellet): a broad band at 3348 cm^{-1} $\nu(O_{11}$-H)+$\nu(O_{12}$-H)+$\nu(O_{2''}$-H)+$\nu(O_{4''}$-H), 2638 cm^{-1} $\nu(O_6$-H), 1728 cm^{-1} $\nu(C_1{=}O)_{lactone}$, 1665 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 882.4823; Elemental analysis $C_{42}H_{79}BrN_2O_{12}$: calculated: C=57.07%; H=9.01%; Br=9.04%; N=3.17%; measured: C=57.11%; H=9.02%; Br=9.01%; N=3.21%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

3c Yield: 96%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.67 (s, 1H), 5.84 (d, ^3J=5.4 Hz, 1H), 5.42 (t, ^3J=7.4 Hz, 1H), 4.86 (m, 1H), 4.75 (m, 1H), 4.45 (d, ^3J=6.9 Hz, 1H), 4.31 (s, 1H), 4.30 (m, 1H), 4.27 (m, 1H), 4.26 (dd, ^2J=12.6 Hz, ^3J=8.4 Hz, 1H), 4.17 (dd, ^2J=13.0 Hz, ^3J=8.2 Hz, 1H), 4.15 (m, 1H), 4.02 (dq, ^3J=9.4 Hz, 6.4 Hz, 1H), 3.74 (m, 1H), 3.56 (m, 1H), 3.54 (m, 1H), 3.45 (m, 1H), 3.44 (d, ^3J=8.2 Hz, 1H), 3.24 (s, 3H), 3.01 (s, 3H), 2.97 (s, 3H), 2.94 (m, 1H), 2.67 (m, 2H), 2.37 (d, ^2J=12.5 Hz, 1H), 2.27 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.12 (m, 1H), 2.03 (d, ^3J=10.2 Hz, 1H), 1.92 (m, 1H), 1.91 (m, 1H), 1.82 (s, 3H), 1.78 (m, 1H), 1.75 (s, 3H), 1.56 (m, 2H), 1.54 (m, 1H), 1.35 (m, 1H), 1.30 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 1.14 (d, ^3J=6.1 Hz, 1H), 1.14 (d, ^3J=6.1 Hz, 3H), 1.09 (d, ^3J=7.3 Hz, 3H), 1.04 (s, 3H), 1.02 (d, ^3J=6.7 Hz, 3H), 0.93 (d, ^3J=7.2 Hz, 3H), 0.85 (d, ^3J=6.5 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 145.8, 112.3, 101.1, 94.4, 83.4, 77.3, 77.1, 76.3, 75.0, 73.6, 72.9, 72.4, 70.6, 69.8, 68.7, 65.7, 64.8, 62.8, 61.5, 49.1, 48.7, 47.1, 44.6, 41.6, 41.6, 35.8, 34.5, 32.4, 27.5, 26.1, 26.1, 22.2, 21.1, 21.0, 21.0, 18.4, 18.4, 17.7, 14.8, 11.0, 9.1, 6.7; FT-IR (KBr pellet): a broad band at 3338 cm^{-1} $\nu(O_{11}$-H)+$\nu(O_{12}$-H)+$\nu(O_{2''}$-H)+$\nu(O_{4''}$-H), 2635 cm^{-1} $\nu(O_6$-H), 1728 cm^{-1} $\nu(C_1{=}O)_{lactone}$, 1666 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 896.4986; Elemental analysis $C_{43}H_{81}BrN_2O_{12}$: calculated: C=57.51%; H=9.09%; Br=8.90%; N=3.12%; measured: C=57.53%; H=9.04%; Br=8.91%; N=3.16%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 96%;

3e Yield: 98%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.68 (s, 1H), 5.88 (d, ^3J=5.4 Hz, 1H), 4.86 (m, 1H), 4.75 (m, 1H), 4.60 (dd, ^2J=16.3 Hz, ^4J=2.5 Hz, 1H), 4.53 (dd, ^2J=16.1 Hz, ^4J=2.6 Hz, 1H), 4.44 (d, ^3J=6.9 Hz, 1H), 4.31 (s, 1H), 4.30 (d, ^3J=6.0 Hz, 1H), 4.23 (d, ^3J=7.6 Hz, 1H), 4.18 (t, ^4J=2.4 Hz, 1H), 4.15 (m, 1H), 4.02 (dq, ^3J=9.4 Hz, 6.4 Hz, 1H), 3.74 (m, 1H), 3.55 (m, 1H), 3.53 (d, ^3J=6.9 Hz, 1H), 3.45 (m, 1H), 3.44 (d, ^3J=8.4 Hz, 1H), 3.24 (s, 3H), 3.01 (s, 3H), 2.97 (s, 3H), 2.94 (dd, ^3J=9.4 Hz, 7.6 Hz, 1H), 2.67 (m, 2H), 2.36 (m, 1H), 2.27 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.12 (m, 1H), 2.03 (d, ^3J=10.2 Hz, 1H), 1.92 (m, 1H), 1.91 (m, 1H),

1.79 (m, 1H), 1.58 (m, 1H), 1.56 (m, 1H), 1.54 (m, 1H), 1.37 (m, 1H), 1.30 (m, 1H), 1.17 (s, 3H), 1.16 (d, ^3J=6.5 Hz, 1H), 1.15 (s, 3H), 1.14 (d, ^3J=6.1 Hz, 3H), 1.09 (d, ^3J=7.5 Hz, 3H), 1.04 (s, 3H), 1.02 (d, ^3J=6.7 Hz, 3H), 0.93 (d, ^3J=7.2 Hz, 3H), 0.85 (d, ^3J=6.5 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 101.1, 94.4, 83.4, 83.1, 77.3, 77.1, 76.3, 75.0, 73.6, 72.9, 72.9, 72.4, 70.6, 69.7, 68.7, 65.7, 64.7, 61.5, 55.2, 49.1, 48.7, 47.1, 44.5, 41.6, 41.5, 35.7, 34.5, 32.3, 27.4, 26.1, 22.2, 21.1, 21.0, 21.0, 18.4, 17.7, 14.8, 10.9, 9.1, 6.7; FT-IR (KBr pellet): a broad band at 3392 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 2125 cm^{-1} ν(C≡C), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 866.4503; Elemental analysis $C_{41}H_{75}BrN_2O_{12}$: calculated: C=56.74%; H=8.71%; Br=9.21%; N=3.23%; measured: C=56.75%; H=8.70%; Br=9.19%; N=3.20%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 99%;

3f Yield: 89%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.62 (s, 1H), 5.80 (d, ^3J=4.0 Hz, 1H), 4.83 (d, ^3J=4.8 Hz, 1H), 4.83 (d, ^2J=15.8 Hz, 1H), 4.74 (m, 1H), 4.53 (d, ^2J=16.1 Hz, 1H), 4.42 (d, ^3J=7.0 Hz, 1H), 4.32 (m, 2H), 4.31 (s, 1H), 4.12 (m, 1H), 4.01 (dq, ^3J=12.3 Hz, 6.2 Hz, 1H), 3.77 (m, 1H), 3.56 (m, 1H), 3.54 (m, 1H), 3.52 (d, ^3J=5.9 Hz, 1H), 3.44 (d, ^3J=8.4 Hz, 1H), 3.26 (s, 3H), 3.25 (s, 3H), 3.21 (s, 3H), 2.95 (dd, ^3J=9.5 Hz, 7.2 Hz, 1H), 2.93 (s, 3H), 2.86 (s, 3H), 2.68 (m, 1H), 2.65 (m, 1H), 2.38 (m, 1H), 2.26 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.13 (m, 1H), 2.01 (dd, ^3J=10.5 Hz, 3.9 Hz, 1H), 1.92 (m, 2H), 1.79 (dqd, ^2J=15.1 Hz, ^3J=7.5 Hz, 2.7 Hz, 1H), 1.59 (m, 2H), 1.53 (dd, ^2J=14.8 Hz, ^3J=4.9 Hz, 1H), 1.37 (ddd, ^2J=15.0 Hz, ^3J=10.1 Hz, 7.1 Hz, 1H), 1.26 (m, 1H), 1.17 (d, ^3J=7.0 Hz, 1H), 1.15 (s, 6H), 1.15 (d, ^3J=6.0 Hz, 3H), 1.04 (d, ^3J=7.1 Hz, 3H), 1.03 (s, 3H),0.94 (d, ^3J=7.1 Hz, 3H), 0.92 (d, ^3J=7.5 Hz, 3H), 0.87 (d, ^3J=6.0 Hz, 3H), 0.79 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 164.0, 101.1, 94.4, 83.3, 77.2, 77.2, 76.3, 75.0, 73.6, 72.9, 72.4, 70.4, 69.5, 68.7, 65.6, 64.7, 63.8, 61.5, 50.7, 49.8, 48.6, 44.5, 41.7, 41.5, 36.1, 35.8, 35.1, 34.6, 32.2, 27.4, 26.1, 22.2, 21.1, 21.1, 20.9, 18.5, 17.7, 14.7, 11.0, 9.2, 6.7; FT-IR (KBr pellet): a broad band at 3402 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2636 cm^{-1} ν(O_6-H), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1657 cm^{-1} ν(C=O)$_{amide}$, 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 913.4887; Elemental analysis $C_{42}H_{80}BrN_3O_{13}$: calculated: C=55.13%; H=8.81%; Br=8.73%; N=4.59%; measured: C=55.15%; H=8.79%; Br=8.71%; N=4.62%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 93%;

3g Yield: 45%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.81 (s, 1H), 5.76 (bs, 1H), 4.87 (m, 1H), 4.80 (m, 1H), 4.60 (m, 1H), 4.36 (m, 1H), 4.32 (m, 2H), 4.30 (m, 1H), 4.18 (m, 1H), 4.00 (m, 1H), 3.80 (m, 1H), 3.70 (m, 1H), 3.60 (m, 1H), 3.57 (m, 1H), 3.48 (m, 1H), 3.42 (d, ^3J=8.4 Hz, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 3.23 (s, 3H), 2.95 (dd, ^3J=9.4 Hz, 7.3 Hz, 1H), 2.68 (m, 1H), 2.67 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 2.27 (d, ^2J=15.2 Hz, 1H), 2.21 (s, 3H), 2.13 (m, 1H), 1.96 (m, 1H), 1.90 (m, 1H), 1.77 (m, 1H), 1.67 (m, 1H), 1.60 (m, 1H), 1.53 (d, ^2J=14.5 Hz, 1H), 1.39 (m, 1H), 1.27 (m, 1H), 1.22 (m, 1H), 1.20 (s, 3H), 1.17 (d, ^3J=6.3 Hz, 3H), 1.15 (s, 3H), 1.08 (d, ^3J=7.5 Hz, 3H), 1.02 (s, 3H), 0.94 (d, ^3J=7.1 Hz, 3H), 0.92 (d, ^3J=8.6 Hz, 3H), 0.87 (d, ^3J=6.8 Hz, 3H), 0.79 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 165.3, 98.3, 94.4, 83.5, 77.2, 77.1, 76.4, 75.0, 74.5, 73.6, 72.8, 72.3, 68.6, 66.5, 66.0, 64.8, 61.5, 59.5, 53.9, 52.9, 49.0, 46.7, 44.5, 41.6, 41.4, 35.7, 34.6, 29.7, 27.4, 26.1, 22.1, 21.1, 20.9, 20.7, 18.6, 17.7, 14.8, 10.9, 8.6, 6.6; FT-IR (KBr pellet): a broad band at 3402 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2636 cm^{-1} ν(O_6-H), 1766 cm^{-1} ν(C=O), 1728 cm^{-1} ν(C_1=O)$_{lactone}$, 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 900.4558; Elemental analysis $C_{41}H_{77}BrN_2O_{14}$: calculated: C=54.60%; H=8.60%; Br=8.86%; N=3.11%; measured: C=54.59%; H=8.62%; Br=8.83%; N=3.14%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 64%;

3gh' Yield: 40%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.81 (s, 1H), 4.94 (m, 1H), 4.87 (m, 1H), 4.80 (m, 1H), 4.60 (m, 1H), 4.36 (m, 1H), 4.32 (m, 3H), 4.30 (m, 1H), 4.18 (m, 1H), 4.00 (m, 1H), 3.70 (m, 1H), 3.57 (m, 1H), 3.48 (m, 1H), 3.42 (d, ^3J=8.4 Hz, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 3.23 (s, 3H), 2.95 (dd, ^3J=9.4 Hz, 7.3 Hz, 1H), 2.68 (m, 1H), 2.67 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 2.27 (d, ^2J=15.2 Hz, 1H), 2.21 (s, 3H), 2.13 (m, 1H), 1.96 (m, 1H), 1.90 (m, 2H), 1.77 (m, 1H), 1.60 (m, 1H), 1.53 (d, ^2J=14.5 Hz, 1H), 1.39 (m, 1H), 1.27 (m, 1H), 1.22 (m, 1H), 1.20 (s, 3H), 1.17 (d, ^3J=6.3 Hz, 3H), 1.15 (s, 3H), 1.08 (d, ^3J=7.5 Hz, 3H), 1.02 (s, 3H), 0.94 (d, ^3J=7.1 Hz, 3H), 0.92 (d, ^3J=8.6 Hz, 3H), 0.87 (d, ^3J=6.8 Hz, 3H), 0.79 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 160.1, 98.3, 94.4, 83.5, 77.2, 77.1, 76.4, 75.0, 74.5, 73.6, 73.6, 72.8, 68.6, 66.5, 66.0, 64.8, 61.5, 54.9, 53.9, 52.9, 49.0, 44.5, 41.6, 41.6, 35.7, 34.6, 29.7, 27.4, 26.1, 22.1, 21.1, 20.9, 20.7, 18.6, 17.7, 14.8, 10.9, 8.6, 6.6; FT-IR (KBr pellet): a broad band at 3397 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 1766 cm^{-1} ν(C=O), 1728 cm^{-1} ν(C_1=O)$_{lactone}$, 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 869.9169; Elemental analysis $C_{40}H_{73}BrN_2O_{13}$: calculated: C=55.23%; H=8.46%; Br=9.19%; N=3.22%; measured: C=55.24%; H=8.47%; Br=9.18%; N=3.20%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 38%;

3i Yield: 95%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.85 (dd, ^3J=3.0 Hz, ^4J=1.2 Hz, 1H), 7.70 (dd, ^3J=5.0 Hz, ^4J=2.9 Hz, 1H), 7.68 (s, 1H), 7.30 (dd, ^3J=5.0 Hz, ^4J=1.3 Hz, 1H), 6.00 (d, ^3J=5.5 Hz, 1H), 4.98 (d, ^2J=12.6 Hz, 1H), 4.86 (d, ^3J=4.8 Hz, 1H), 4.75 (dd, ^3J=10.2 Hz, 2.8 Hz, 1H), 4.73 (d, ^2J=12.1 Hz, 1H), 4.44 (d, ^3J=7.0 Hz, 1H), 4.32 (s, 1H), 4.31 (d, ^3J=8.0 Hz, 1H), 4.20 (d, ^3J=7.6 Hz, 1H), 4.19 (m, 1H), 4.01 (dq, ^3J=9.2 Hz, 6.1 Hz, 1H), 3.67 (m, 2H), 3.57 (d, ^3J=7.1 Hz, 1H), 3.44 (m, 1H), 3.44 (d, ^3J=8.4 Hz, 1H), 3.21 (s, 3H), 3.07 (s, 3H), 2.99 (s, 3H), 2.92 (dd, ^3J=9.5 Hz, 7.4 Hz, 1H), 2.68 (m, 2H), 2.38 (d, ^2J=11.8 Hz, 1H), 2.28 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.13 (t, ^2J=11.7 Hz, 1H), 2.04 (dd, ^3J=10.8 Hz, 4.1 Hz, 1H), 1.94 (m, 1H), 1.90 (m, 1H), 1.78 (dqd, ^2J=15.0 Hz, ^3J=7.5 Hz, 2.8 Hz, 1H), 1.58 (d, ^3J=10.4 Hz, 1H), 1.52 (dd, ^2J=15.1 Hz, ^3J=5.1 Hz, 1H), 1.50 (d, ^2J=14.8 Hz, 1H), 1.37 (ddd, ^2J=14.2 Hz, ^3J=10.1 Hz, 7.2 Hz, 1H), 1.29 (dd, ^2J=14.9 Hz, ^3J=7.9 Hz, 1H), 1.19 (s, 3H), 1.15 (d, ^3J=6.2 Hz, 3H), 1.13 (s, 3H), 1.13 (d, ^3J=6.1 Hz, 3H), 1.10 (d, ^3J=7.5 Hz, 3H), 1.03 (s, 3H), 0.99 (d, ^3J=7.5 Hz, 3H), 0.95 (d, ^3J=6.7 Hz, 3H), 0.86 (d, ^3J=7.1 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 131.9, 130.7, 128.9, 127.5, 101.1, 94.4, 83.0, 77.2, 77.1, 76.3, 75.0, 73.6, 72.8, 72.5, 70.7, 69.1, 68.7, 65.8, 64.7, 62.2, 61.5, 49.7, 49.1, 47.4, 44.7, 41.7, 41.7, 35.7, 34.5, 32.2, 27.5, 26.1, 22.2, 21.1, 20.9, 20.9, 18.6, 17.7, 14.8, 10.9, 9.0, 6.7; FT-IR (KBr pellet): a broad band at 3388 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 924.4381; Elemental analysis $C_{43}H_{77}BrN_2O_{12}S$: calculated: C=55.77%; H=8.38%; Br=8.63%; N=3.03%; S=3.46%; measured: C=55.76%; H=8.38%; Br=8.61%; N=3.02%; S=3.47%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 95%;

3j Yield: 93%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.79 (d, ^3J=5.7 Hz, 1H), 7.67 (s, 1H), 7.27 (d, ^3J=5.6 Hz, 1H), 6.12 (d, ^3J=5.0 Hz, 1H), 4.89 (d, ^2J=12.6 Hz, 1H), 4.87 (d, ^3J=4.2 Hz, 1H), 4.75 (dd, ^3J=10.0 Hz, 2.8 Hz, 1H), 4.64 (d, ^2J=13.1 Hz, 1H), 4.50 (d, ^3J=6.7 Hz, 1H), 4.32 (s, 1H), 4.30 (d, ^3J=8.4 Hz, 1H), 4.21 (d, ^3J=7.5 Hz, 1H), 4.18 (d, ^3J=3.0 Hz, 1H), 4.02 (dq, ^3J=12.4 Hz, 6.4 Hz, 1H), 3.74 (m, 1H), 3.68 (m, 1H), 3.63 (m, 1H), 3.58 (d, ^3J=7.0 Hz, 1H), 3.45 (d, ^3J=8.2 Hz, 1H), 3.27 (s, 3H), 3.06 (s, 6H), 2.95 (dd, ^3J=9.5 Hz, 7.5 Hz, 1H), 2.69 (m, 2H), 2.39 (d, ^2J=12.1 Hz, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.20 (s, 3H), 2.15 (m, 1H), 2.14 (m, 1H), 1.95 (m, 1H), 1.92 (m, 1H), 1.79 (dqd, ^2J=15.2 Hz, ^3J=7.5 Hz, 2.8 Hz, 1H), 1.67 (m, 1H), 1.61 (d, ^2J=14.6 Hz, 1H), 1.54 (dd, ^2J=14.9 Hz, ^3J=4.6 Hz, 1H), 1.38 (ddd, ^2J=14.2 Hz, ^3J=10.1 Hz, 7.2 Hz, 1H), 1.33 (m, 1H), 1.20 (s, 3H), 1.17 (d, ^3J=6.4 Hz, 1H), 1.16 (d, ^3J=6.4 Hz, 3H), 1.16 (s, 3H), 1.10 (d, ^3J=7.5 Hz, 3H), 1.03 (s, 3H), 0.98 (d, ^3J=7.7 Hz, 3H), 0.95 (d, ^3J=7.0 Hz, 3H), 0.87 (d, ^3J=7.0 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 131.4, 129.0, 128.4, 118.8, 101.2, 94.4, 83.3, 77.3, 77.1, 76.3, 75.0, 73.6, 72.8, 72.5, 71.7, 70.8, 68.7, 65.8, 64.8, 61.5, 59.9, 50.3, 49.0, 47.8, 44.7, 41.7, 41.6, 35.7, 34.5, 32.6, 27.5, 26.1, 22.0, 21.1, 21.0, 20.9, 18.5, 17.7, 14.8, 11.0, 9.1, 6.7; FT-IR (KBr pellet): a broad band at 3393 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2636 cm^{-1} ν(O_6-H), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O), 795 cm^{-1} ν(C-Br); HR-MALDI-TOF [M+H]$^+$ = 1004.3465; Elemental analysis $C_{43}H_{76}Br_2N_2O_{12}S$: calculated: C=51.39%; H=7.62%; Br=15.90%; N=2.79%; S=3.19%; measured: C=51.40%; H=7.62%; Br=15.89%;

N=2.81%; S=3.18%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 93%;

3k Yield: 87%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.76 (d, ^3J=3.8 Hz, 1H), 7.67 (s, 1H), 7.10 (d, ^3J=3.8 Hz, 1H), 6.12 (d, ^3J=5.1 Hz, 1H), 5.12 (d, ^2J=14.0 Hz, 1H), 5.07 (d, ^2J=14.0 Hz, 1H), 4.88 (d, ^3J=4.8 Hz, 1H), 4.76 (d, ^3J=10.0 Hz, 1H), 4.45 (d, ^3J=6.8 Hz, 1H), 4.32 (m, 1H), 4.31 (s, 1H), 4.26 (d, ^3J=7.0 Hz, 1H), 4.18 (m, 1H), 4.03 (dq, ^3J=9.4 Hz, 6.2 Hz, 1H), 3.71 (m, 1H), 3.62 (m, 1H), 3.57 (d, ^3J=7.3 Hz, 1H), 3.55 (m, 1H), 3.45 (d, ^3J=8.2 Hz, 1H), 3.23 (s, 3H), 3.15 (s, 3H), 3.14 (s, 3H), 2.95 (dd, ^3J=9.3 Hz, 6.9 Hz, 1H), 2.70 (m, 2H), 2.37 (m, 1H), 2.28 (d, ^2J=15.1 Hz, 1H), 2.23 (s, 3H), 2.14 (m, 1H), 2.03 (m, 1H), 1.95 (m, 1H), 1.93 (m, 1H), 1.79 (dqd, ^2J=15.1 Hz, ^3J=7.5 Hz, 2.6 Hz, 1H), 1.60 (m, 1H), 1.60 (d, ^2J=12.7 Hz, 1H), 1.54 (dd, ^2J=15.2 Hz, ^3J=5.1 Hz, 1H), 1.38 (ddd, ^2J=14.8 Hz, ^3J=10.1 Hz, 7.2 Hz, 1H), 1.38 (m, 1H), 1.25 (d, ^3J=6.4 Hz, 1H), 1.20 (s, 3H), 1.17 (d, ^3J=6.3 Hz, 3H), 1.14 (s, 3H), 1.11 (d, ^3J=7.4 Hz, 3H), 1.04 (s, 3H), 0.98 (d, ^3J=7.5 Hz, 3H), 0.98 (d, ^3J=7.5 Hz, 3H), 0.88 (d, ^3J=6.7 Hz, 3H), 0.81 (t, ^3J=7.5 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 153.8, 146.6, 120.3, 113.1, 100.9, 94.4, 82.9, 77.1, 77.1, 76.3, 75.0, 74.5, 73.6, 72.8, 72.8, 70.7, 70.5, 68.7, 65.7, 64.7, 61.6, 60.0, 50.2, 48.9, 44.6, 41.6, 41.6, 35.8, 34.6, 32.3, 27.4, 26.1, 22.1, 21.1, 21.0, 20.9, 18.5, 17.7, 14.7, 11.0, 9.0, 6.8; FT-IR (KBr pellet): a broad band at 3393 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 1725 cm^{-1} ν(C_1=O)$_{lactone}$, 1504 cm^{-1} ν(NO_2); 1457 cm^{-1} ν(C=C), 1352 cm^{-1} ν(NO_2), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 953.4460; Elemental analysis $C_{43}H_{76}BrN_3O_{15}$: calculated: C=54.08%; H=8.02%; Br=8.37%; N=4.40%; measured: C=54.10%; H=8.03%; Br=8.36%; N=4.41%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 94%;

3l Yield: 95%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.66 (s, 1H), 7.61 (d, ^3J=7.0 Hz, 2H), 7.54 (t, ^3J=7.3 Hz, 1H), 7.48 (t, ^3J=7.4 Hz, 2H), 6.13 (d, ^3J=5.4 Hz, 1H), 4.98 (d, ^2J=12.3 Hz, 1H), 4.87 (d, ^3J=4.7 Hz, 1H), 4.75 (dd, ^3J=10.1 Hz, 2.8 Hz, 1H), 4.75 (d, ^2J=11.8 Hz, 1H), 4.66 (d, ^3J=7.0 Hz, 1H), 4.31 (s, 1H), 4.31 (d, ^3J=8.3 Hz, 1H), 4.20 (m, 2H), 4.02 (dq, ^3J=12.4 Hz, 6.2 Hz, 1H), 3.67 (m, 2H), 3.58 (d, ^3J=7.0 Hz, 1H), 3.50 (m, 1H), 3.45 (d, ^3J=8.3 Hz, 1H), 3.23 (s, 3H), 3.07 (s, 3H), 2.98 (s, 3H), 2.92 (dd, ^3J=9.4 Hz, 7.4 Hz, 1H), 2.69 (m, 2H), 2.38 (d, ^2J=11.8 Hz, 1H), 2.28 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.04 (m, 1H), 2.13 (d, ^2J=11.7 Hz, 1H), 1.96 (m, 1H), 1.92 (m, 1H), 1.78 (ddq, ^2J=14.7 Hz, ^3J=7.5 Hz, 2.8 Hz, 1H), 1.61 (m, 2H), 1.52 (dd, ^2J=14.9 Hz, ^3J=5.0 Hz, 1H), 1.37 (ddd, ^2J=14.4 Hz, ^3J=10.1 Hz, 7.2 Hz, 1H), 1.31 (dd, ^2J=14.7 Hz, ^3J=8.0 Hz, 1H), 1.19 (s, 3H), 1.15 (d, ^3J=6.2 Hz, 3H), 1.13 (s, 3H), 1.12 (d, ^3J=6.6 Hz, 1H), 1.11 (d, ^3J=7.0 Hz, 3H), 1.03 (s, 3H), 1.00 (d, ^3J=7.6 Hz, 3H), 0.95 (d, ^3J=6.6 Hz, 3H), 0.86 (d, ^3J=6.8 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 133.5, 133.5, 130.2, 128.8, 128.8, 128.5, 101.1, 94.4, 83.0, 77.2, 77.1, 76.3, 75.0, 73.6, 72.8, 72.5, 70.8, 69.5, 68.8, 67.2, 65.8, 64.7, 61.5, 49.5, 49.0, 47.5, 44.7, 41.7, 41.7, 35.7, 34.5, 32.3, 27.5, 26.1, 22.2, 21.1, 20.9, 20.9, 18.6, 17.7, 14.8, 10.9, 9.0, 6.7; FT-IR (KBr pellet): a broad band at 3380 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 26376 cm^{-1} ν(O_6-H), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1456 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 918.4816; Elemental analysis $C_{45}H_{79}BrN_2O_{12}$: calculated: C=58.75%; H=8.65%; Br=8.69%; N=3.04%; measured: C=58.76%; H=8.63%; Br=8.67%; N=3.05%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

3m Yield: 92%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.15 (d, ^3J=7.4 Hz, 1H), 7.84 (m, 3H), 7.67 (s, 1H), 6.11 (d, ^3J=4.2 Hz, 1H), 5.40 (d, ^2J=13.2 Hz, 1H), 5.01 (d, ^2J=13.2 Hz, 1H), 4.87 (d, ^3J=4.8 Hz, 1H), 4.75 (dd, ^3J=10.0 Hz, 2.9 Hz, 1H), 4.50 (d, ^3J=5.8 Hz, 1H), 4.31 (s, 1H), 4.30 (d, ^3J=8.2 Hz, 1H), 4.23 (d, ^3J=7.4 Hz, 1H), 4.17 (m, 1H), 4.04 (dq, ^3J=12.5 Hz, 6.4 Hz, 1H), 3.74 (m, 1H), 3.68 (m, 2H), 3.56 (d, ^3J=6.9 Hz, 1H), 3.45 (d, ^3J=8.2 Hz, 1H), 3.26 (s, 3H), 2.97 (s, 3H), 2.96 (m, 1H), 2.95 (s, 3H), 2.70 (m, 1H), 2.67 (m, 1H), 2.38 (d, ^2J=11.7 Hz, 1H), 2.28 (d, ^2J=15.1 Hz, 1H), 2.21 (s, 3H), 2.15 (d, ^2J=11.7 Hz, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.92 (m, 1H), 1.78 (ddq, ^2J=14.8 Hz, ^3J=7.6 Hz, 2.8 Hz, 1H), 1.66 (d, ^3J=11.1 Hz, 1H), 1.59 (m, 1H), 1.51 (dd, ^2J=15.0 Hz, ^3J=4.9 Hz, 1H), 1.34 (ddd, ^2J=14.3 Hz, ^3J=10.0 Hz, 7.2 Hz, 1H), 1.30 (m, 1H), 1.19 (s, 3H), 1.17 (d, ^3J=6.0 Hz, 1H), 1.16 (s, 3H), 1.15 (d, ^3J=6.2 Hz, 3H), 1.10 (d, ^3J=7.4 Hz, 3H), 1.03 (s, 3H), 0.98 (d, ^3J=7.5 Hz, 3H), 0.95 (d, ^3J=6.8 Hz, 3H), 0.86 (d, ^3J=6.7 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 151.1, 136.7, 133.6, 132.2, 125.8, 121.5, 101.1, 94.4, 83.2, 77.3, 77.1, 76.3, 75.0, 73.6, 73.5, 72.8, 72.5, 70.8, 68.7, 65.7, 64.8, 61.5, 60.9, 50.1, 49.0, 47.1, 44.6, 41.6, 41.6, 35.8, 34.6, 32.2, 27.4, 26.1, 22.2, 21.1, 21.0, 20.9, 18.5, 17.7, 14.8, 11.0, 9.1, 6.7; FT-IR (KBr pellet): a broad band at 3397 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 265 cm^{-1} ν(O_6-H), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1533 cm^{-1} ν(NO_2), 1457 cm^{-1} ν(C=C), 1347 cm^{-1} ν(NO_2), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 963.4676; Elemental analysis $C_{45}H_{78}BrN_3O_{14}$: calculated: C=56.01%; H=8.15%; Br=8.28%; N=4.35%; measured: C=56.02%; H=8.14%; Br=8.30%; N=4.34%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

3n Yield: 86%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.53 (s, 3H), 8.40 (dd, ^3J=8.3 Hz, ^4J=1.6 Hz, 1H), 8.05 (d, ^3J=7.7 Hz, 1H), 7.80 (t, ^3J=8.0 Hz, 1H), 7.67 (s, 1H), 6.21 (d, ^3J=5.5 Hz, 1H), 5.10 (d, ^2J=12.4 Hz, 1H), 4.91 (d, ^2J=12.4 Hz, 1H), 4.87 (d, ^3J=4.8 Hz, 1H), 4.74 (dd, ^3J=10.0 Hz, 2.9 Hz, 1H), 4.45 (d, ^3J=7.0 Hz, 1H), 4.32 (s, 1H), 4.31 (d, ^3J=11.9 Hz, 1H), 4.22 (d, ^3J=7.4 Hz, 1H), 4.20 (m, 1H), 4.02 (dq, ^3J=12.3 Hz, 6.2 Hz, 1H), 3.70 (m, 1H), 3.67 (m, 1H), 3.59 (d, ^3J=7.1 Hz, 1H), 3.48 (m, 1H), 3.45 (d, ^3J=8.4 Hz, 1H), 3.14 (s, 3H), 3.11 (s, 3H), 3.05 (s, 3H), 2.92 (dd, ^3J=9.4 Hz, 7.2 Hz, 1H), 2.70 (m, 1H), 2.68 (m, 1H), 2.38 (d, ^2J=11.8 Hz, 1H), 2.26 (d, ^2J=15.1 Hz, 1H), 2.23 (d, ^3J=11.0 Hz, 1H), 2.22 (s, 3H), 2.14 (d, ^2J=11.7 Hz, 1H), 1.96 (m, 1H), 1.91 (m, 1H), 1.78 (dqd, ^2J=15.2 Hz, ^3J=7.5 Hz, 2.8 Hz, 1H), 1.66 (m, 1H), 1.60 (m, 1H), 1.52 (dd, ^2J=14.9 Hz, ^3J=5.0 Hz, 1H), 1.38 (ddd, ^2J=14.5 Hz, ^3J=10.2 Hz, 7.4 Hz, 1H), 1.32 (m, 1H), 1.19 (s, 3H), 1.15 (d, ^3J=6.2 Hz, 3H), 1.14 (d, ^3J=6.8 Hz, 3H), 1.11 (d, ^3J=7.6 Hz, 3H), 1.10 (s, 3H), 1.03 (s, 3H), 1.02 (d, ^3J=7.5 Hz, 3H), 0.95 (d, ^3J=6.6 Hz, 3H), 0.87 (d, ^3J=6.8 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 147.9, 139.8, 130.4, 130.4, 128.4, 125.0, 101.0, 94.4, 82.8, 77.1, 77.1, 76.3, 75.0, 73.6, 72.8, 72.5, 70.7, 70.1, 68.7, 65.8, 65.7, 64.7, 61.5, 49.6, 48.8, 47.6, 44.6, 41.7, 41.7, 35.7, 34.6, 32.3, 27.4, 26.1, 22.2, 21.1, 20.9, 20.9, 18.6, 17.7, 14.7, 11.0, 9.0, 6.7; FT-IR (KBr pellet): a broad band at 3396 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 1726 cm^{-1} ν(C_1=O)$_{lactone}$, 1534 cm^{-1} ν(NO_2), 1457 cm^{-1} ν(C=C), 1352 cm^{-1} ν(NO_2), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 963.4676; Elemental analysis $C_{45}H_{78}BrN_3O_{14}$: calculated: C=56.01%; H=8.15%; Br=8.28%; N=4.35%; measured: C=56.00%; H=8.13%; Br=8.29%; N=4.32%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

3o Yield: 89%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.33 (t, ^3J=8.3 Hz, 2H), 7.88 (d, ^3J=8.4 Hz, 2H), 7.67 (s, 1H), 6.16 (d, ^3J=5.5 Hz, 1H), 5.03 (d, ^2J=12.3 Hz, 1H), 4.92 (d, ^2J=12.3 Hz, 1H), 4.87 (d, ^3J=4.8 Hz, 1H), 4.75 (dd, ^3J=10.1 Hz, 2.8 Hz, 1H), 4.47 (d, ^3J=7.0 Hz, 1H), 4.31 (s, 1H), 4.30 (d, ^3J=8.4 Hz, 1H), 4.21 (d, ^3J=7.4 Hz, 1H), 4.19 (m, 1H), 4.03 (dq, ^3J=12.6 Hz, 6.4 Hz, 1H), 3.68 (m, 2H), 3.57 (d, ^3J=7.0 Hz, 1H), 3.52 (m, 1H), 3.44 (d, ^3J=8.3 Hz, 1H), 3.24 (s, 3H), 3.09 (s, 3H), 3.03 (s, 3H), 2.92 (dd, ^3J=9.4 Hz, 7.3 Hz, 1H), 2.68 (m, 2H), 2.38 (d, ^2J=11.8 Hz, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.13 (t, ^2J=11.6 Hz, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.91 (m, 1H), 1.78 (ddq, ^2J=14.8 Hz, ^3J=7.5 Hz, 2.8 Hz, 1H), 1.61 (m, 2H), 1.53 (dd, ^2J=14.9 Hz, ^3J=4.9 Hz, 1H), 1.38 (ddd, ^2J=14.3 Hz, ^3J=10.0 Hz, 7.2 Hz, 1H), 1.31 (dd, ^2J=14.6 Hz, ^3J=7.8 Hz, 1H), 1.19 (s, 3H), 1.15 (d, ^3J=6.1 Hz, 6H), 1.14 (d, ^3J=6.6 Hz, 3H), 1.14 (s, 3H), 1.11 (d, ^3J=7.6 Hz, 3H), 1.03 (s, 3H), 1.00 (d, ^3J=7.6 Hz, 3H), 0.95 (d, ^3J=6.6 Hz, 3H), 0.86 (d, ^3J=6.8 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 148.5, 135.6, 135.0, 135.0, 123.7, 123.7, 101.1, 94.5, 83.2, 77.3,77.1, 76.4, 75.0, 73.6, 72.9, 72.5, 70.7, 70.7, 68.7, 65.7, 65.5, 64.8, 61.5, 49.7, 49.0, 47.9, 44.7, 41.7, 41.7, 35.7, 34.6, 32.4, 27.5, 26.1, 22.2, 21.1, 20.9, 20.9, 18.5, 17.7, 14.8, 11.0, 9.2, 6.7; FT-IR (KBr pellet): a broad band at 3388 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 1726 cm^{-1} ν(C_1=O)$_{lactone}$, 1527 cm^{-1} ν(NO_2), 1457 cm^{-1} ν(C=C), 1348 cm^{-1} ν(NO_2), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 963.4676; Elemental analysis $C_{45}H_{78}BrN_3O_{14}$: calculated: C=56.01%; H=8.15%; Br=8.28%; N=4.35%;

measured: C=56.01%; H=8.12%; Br=8.26%; N=4.36%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 99%;

3p Yield: 77%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.67 (s, 1H), 7.44 (d, ^3J=8.9 Hz, 1H), 7.43 (d, ^3J=8.9 Hz, 1H), 6.14 (d, ^3J=5.1 Hz, 1H), 5.57 (d, ^2J=13.6 Hz, 1H), 5.31 (d, ^2J=13.4 Hz, 1H), 4.87 (d, ^3J=4.8 Hz, 1H), 4.75 (dd, ^3J=10.0 Hz, 2.9 Hz, 1H), 4.51 (d, ^3J=7.0 Hz, 1H), 4.31 (s, 1H), 4.30 (d, ^3J=7.2 Hz, 1H), 4.18 (d, ^3J=7.6 Hz, 1H), 4.16 (d, ^3J=6.1 Hz, 1H), 4.02 (dq, ^3J=12.5 Hz, 6.3 Hz, 1H), 3.77 (m, 2H), 3.66 (m, 1H), 3.56 (d, ^3J=7.0 Hz, 1H), 3.44 (d, ^3J=8.2 Hz, 1H), 3.28 (s, 3H), 2.99 (s, 6H), 2.95 (m, 1H), 2.67 (m, 2H), 2.38 (dd, ^2J=12.5 Hz, ^3J=2.7 Hz, 1H), 2.28 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.17 (d, ^3J=10.5 Hz, 1H), 2.12 (d, ^2J=12.1 Hz, 1H), 1.94 (m, 1H), 1.91 (m, 1H), 1.77 (dqd, ^2J=14.6 Hz, ^3J=7.4 Hz, 2.8 Hz, 1H), 1.67 (d, ^2J=11.9 Hz, 1H), 1.60 (d, ^2J=14.3 Hz, 1H), 1.55 (dd, ^2J=15.0 Hz, ^3J=4.9 Hz, 1H), 1.38 (ddd, ^2J=14.2 Hz, ^3J=10.0 Hz, 7.2 Hz, 1H), 1.30 (dd, ^2J=14.6 Hz, ^3J=8.2 Hz, 1H), 1.19 (s, 3H), 1.18 (m, 6H), 1.17 (s, 3H), 1.09 (d, ^3J=7.4 Hz, 3H), 1.02 (s, 3H), 0.96 (d, ^3J=7.2 Hz, 3H), 0.95 (d, ^3J=6.7 Hz, 3H), 0.86 (d, ^3J=6.8 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 164.3 (d, ^1J=250.1 Hz), 164.3 (d, ^1J=250.1 Hz), 163.1 (d, ^1J =261.6), 102.5 (d, ^3J =4.0), 101.7 (d, ^2J =25.7), 101.5 (d, ^2J =24.3), 101.2, 94.5, 83.4, 77.3, 77.1, 76.4, 75.0, 73.6, 73.1, 72.8, 72.5, 71.0, 68.7, 67.8, 65.8, 64.8, 61.5, 49.5, 45.3, 44.7, 41.6, 41.6, 35.7, 34.6, 32.0, 27.5, 26.1, 22.2, 21.1, 21.0, 20.9, 18.5, 17.7, 14.8, 11.0, 9.1, 6.7; FT-IR (KBr pellet): a broad band at 3386 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 1726 cm^{-1} ν(C_1=O)$_{lactone}$, 1457 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O), 1001 cm^{-1} ν(C-F); HR-MALDI-TOF $[M+H]^+$ = 972.4534; Elemental analysis $C_{45}H_{76}BrF_3N_2O_{12}$: calculated: C=55.49%; H=7.86%; Br=8.20%; F=5.85%; N=2.88%; measured: C=55.50%; H=7.86%; Br=8.21%; F=5.83%; N=2.90%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 96%;

3r Yield: 83%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.87 (d, ^3J=8.3 Hz, 2H), 7.83 (d, ^3J=8.3 Hz, 2H), 7.67 (s, 1H), 6.16 (d, ^3J=5.5 Hz, 1H), 5.03 (d, ^2J=12.3 Hz, 1H), 4.87 (d, ^3J=5.0 Hz, 1H), 4.86 (d, ^2J=12.0 Hz, 1H), 4.76 (dd, ^3J=10.1 Hz, 2.9 Hz, 1H), 4.47 (d, ^3J=7.0 Hz, 1H), 4.32 (s, 1H), 4.31 (d, ^3J=7.9 Hz, 1H), 4.19 (m, 2H), 4.02 (dq, ^3J=12.4 Hz, 6.2 Hz, 1H), 3.67 (m, 2H), 3.57 (d, ^3J=7.0 Hz, 1H), 3.50 (m, 1H), 3.45 (d, ^3J=8.4 Hz, 1H), 3.21 (s, 3H), 3.10 (s, 3H), 3.03 (s, 3H), 2.99 (d, ^3J=9.4 Hz, 7.3 Hz, 1H), 2.69 (m, 2H), 2.38 (d, ^2J=12.0 Hz, 1H), 2.28 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.14 (t, ^2J=11.7 Hz, 1H), 2.05 (dd, ^3J=10.9 Hz, 4.1 Hz, 1H), 1.95 (m, 1H), 1.91 (m, 1H), 1.78 (dqd, ^2J=15.1 Hz, ^3J=7.5 Hz, 2.7 Hz, 1H), 1.62 (m, 1H), 1.60 (m, 1H), 1.53 (dd, ^2J=14.9 Hz, ^3J=4.9 Hz, 1H), 1.38 (ddd, ^2J=15.1 Hz, ^3J=10.1 Hz, 7.2 Hz, 1H), 1.31 (m, 1H), 1.19 (s, 3H), 1.15 (d, ^3J=6.6 Hz, 3H), 1.14 (d, ^3J=6.6 Hz, 3H), 1.12 (s, 3H), 1.11 (d, ^3J=7.7 Hz, 3H), 1.03 (s, 3H), 1.00 (d, ^3J=7.6 Hz, 3H), 0.95 (d, ^3J=6.7 Hz, 3H), 0.86 (d, ^3J=6.8 Hz, 3H), 0.80 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 134.4, 133.1, 130.2 (q, ^2J =31.8), 133.1, 125.7, 125.6, 123.9 (q, ^1J =272.9), 101.1, 94.4, 83.1, 77.3, 77.1, 76.3, 75.0, 73.6, 72.8, 72.5, 70.7, 70.1, 68.7, 66.1, 65.8, 64.7, 61.5, 49.7, 49.0, 47.8, 44.7, 41.7, 41.7, 35.7, 34.5, 32.3, 27.5, 26.1, 22.2, 21.1, 20.9, 20.9, 18.5, 17.7, 14.8, 10.9, 9.1, 6.7; FT-IR (KBr pellet): a broad band at 3393 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 1726 cm^{-1} ν(C_1=O)$_{lactone}$, 1460 cm^{-1} ν(C=C), 1280 cm^{-1} ν(CF_3), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 986.4690; Elemental analysis $C_{46}H_{78}BrF_3N_2O_{12}$: calculated: C=55.92%; H=7.98%; Br=8.09%; F=5.77%; N=2.84%; measured: C=55.94%; H=8.00%; Br=8.08%; F=5.76%; N=2.84%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 97%;

3s Yield: 81%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.25 (d, ^3J=8.4 Hz, 1H), 8.23 (s, 1H), 8.10 (d, ^3J=8.1 Hz, 1H), 7.67 (s, 1H), 6.14 (d, ^3J=5.0 Hz, 1H), 4.88 (d, ^3J=5.1 Hz, 1H), 4.87 (d, ^2J=13.4 Hz, 1H), 4.75 (dd, ^3J=10.1 Hz, 2.9 Hz, 1H), 4.54 (d, ^3J=6.6 Hz, 1H), 4.43 (d, ^2J=13.7 Hz, 1H), 4.31 (s, 1H), 4.31 (d, ^3J=8.3 Hz, 1H), 4.27 (d, ^3J=7.4 Hz, 1H), 4.17 (d, ^3J=4.7 Hz, 1H), 4.06 (dq, ^3J=12.3 Hz, 6.3 Hz, 1H), 3.79 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.58 (d, ^3J=6.9 Hz, 1H), 3.46 (d, ^3J=8.2 Hz, 1H), 3.28 (s, 3H), 3.05 (s, 3H), 3.04 (s, 3H), 2.97 (dd, ^3J=9.5 Hz, 7.4 Hz, 1H), 2.69 (m, 2H), 2.39 (dd, ^2J=12.2 Hz, ^3J=2.6 Hz, 1H), 2.30 (d, ^2J=11.7 Hz, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.22 (s, 3H), 2.14 (t, ^2J=11.7 Hz, 1H), 1.96 (m, 1H), 1.92 (m, 1H), 1.78 (dqd, ^2J=15.0 Hz, ^3J=7.4 Hz, 2.6 Hz, 1H), 1.71 (d, ^2J=11.7 Hz, 1H), 1.61 (d, ^2J=14.3 Hz, 1H), 1.55 (dd, ^2J=15.0 Hz, ^3J=4.9 Hz, 1H), 1.39 (ddd, ^2J=14.3 Hz, ^3J=10.1 Hz, 7.2 Hz, 1H), 1.32 (m, 1H), 1.21 (s, 3H), 1.20 (d, ^3J=6.4 Hz, 3H), 1.18 (d, ^3J=6.3 Hz, 3H), 1.16 (s, 3H), 1.11 (d, ^3J=7.5 Hz, 3H), 1.03 (s, 3H), 0.98 (d, ^3J=7.8 Hz, 3H), 0.96 (d, ^3J=6.6 Hz, 3H), 0.87 (d, ^3J=6.9 Hz, 3H), 0.81 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 138.2, 132.1 (q, ^2J =32.6), 131.1, 129.5, 129.4 (q, ^2J =30.1), 124.7, 123.5 (q, ^1J =272.3), 123.5 (q, ^1J =272.3), 101.2, 94.4, 83.4, 77.3, 77.1, 76.4, 75.0, 74.7, 73.6, 72.9, 72.5, 70.4, 68.7, 65.8, 64.8, 61.7, 61.5, 50.5, 48.9, 47.2, 44.6, 41.7, 41.6, 35.7, 34.5, 32.3, 27.5, 26.1, 22.2, 21.1, 21.0, 21.0, 18.5, 17.7, 14.8, 11.0, 9.1, 6.7; FT-IR (KBr pellet): a broad band at 3393 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1460 cm^{-1} ν(C=C), 1325 cm^{-1} ν(CF_3), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 1054.4564; Elemental analysis $C_{47}H_{77}BrF_6N_2O_{12}$: calculated: C=53.46%; H=7.35%; Br=7.57%; F=10.79%; N=2.65%; measured: C=53.48%; H=7.33%; Br=7.57%; F=10.80%; N=2.64%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 96%;

3t Yield: 83%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.09 (dd, ^3J=8.0 Hz, ^4J=1.3 Hz, 1H), 7.70 (dd, ^3J=7.8 Hz, ^4J=1.7 Hz, 1H), 7.67 (s, 1H), 7.54 (td, ^3J=7.6 Hz, ^4J=1.3 Hz, 1H), 7.27 (td, ^3J=7.6 Hz, ^4J=1.6 Hz, 1H), 6.08 (d, ^3J=5.1 Hz, 1H), 5.07 (d, ^2J=13.1 Hz, 1H), 4.88 (d, ^3J=4.9 Hz, 1H), 4.75 (dd, ^3J=10.1 Hz, 2.8 Hz, 1H), 4.73 (d, ^2J=13.3 Hz, 1H), 4.55 (d, ^3J=6.7 Hz, 1H), 4.32 (s, 1H), 4.31 (d, ^3J=8.2 Hz, 1H), 4.22 (d, ^3J=7.6 Hz, 1H), 4.18 (d, ^3J=4.7 Hz, 1H), 4.02 (dq, ^3J=12.3 Hz, 6.2 Hz, 1H), 3.77 (m, 1H), 3.75 (m, 1H), 3.70 (m, 1H), 3.56 (d, ^3J=6.9 Hz, 1H), 3.46 (d, ^3J=8.3 Hz, 1H), 3.30 (s, 3H), 3.13 (s, 3H), 3.02 (s, 3H), 2.95 (dd, ^3J=9.5 Hz, 7.6 Hz, 1H), 2.69 (m, 2H), 2.39 (d, ^2J=11.2 Hz, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.25 (m, 1H), 2.22 (s, 3H), 2.12 (t, ^2J=11.7 Hz, 1H), 1.97 (m, 1H), 1.92 (m, 1H), 1.79 (dqd, ^2J=14.4 Hz, ^3J=7.5 Hz, 2.8 Hz, 1H), 1.71 (m, 1H), 1.60 (d, ^2J=14.3 Hz, 1H), 1.55 (dd, ^2J=14.5 Hz, ^3J=5.0 Hz, 1H), 1.39 (ddd, ^2J=14.3 Hz, ^3J=10.1 Hz, 7.3 Hz, 1H), 1.31 (dd, ^2J=14.1 Hz, ^3J=7.7 Hz, 1H), 1.20 (d, ^3J=6.2 Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.17 (d, ^3J=6.8 Hz, 3H), 1.10 (d, ^3J=7.5 Hz, 3H), 1.03 (s, 3H), 0.99 (d, ^3J=7.6 Hz, 3H), 0.96 (d, ^3J=6.8 Hz, 3H), 0.86 (d, ^3J=6.9 Hz, 3H), 0.81 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.1, 141.1, 135.2, 132.2, 131.4, 128.7, 105.3, 101.2, 94.5, 83.5, 77.3, 77.2, 76.4, 75.0, 73.9, 73.6, 72.8, 72.5, 70.3, 68.7, 68.0, 65.8, 64.8, 61.5, 50.9, 49.0, 47.9, 44.6, 41.7, 41.6, 35.8, 34.6, 32.7, 27.5, 26.1, 22.2, 21.1, 21.0, 20.9, 18.5, 17.7, 14.8, 11.0, 9.2, 6.7; FT-IR (KBr pellet): a broad band at 3393 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1460 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O), 640 cm^{-1} ν(C-I); HR-MALDI-TOF $[M+H]^+$ = 1044.3783; Elemental analysis $C_{45}H_{78}BrIN_2O_{12}$: calculated: C=51.68%; H=7.52%; Br=7.64%; I=12.13%; N=2.68%; measured C=51.70%; H=7.51%; Br=7.63%; I=12.12%; N=2.69%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25) purity: 99%;

3u Yield: 88%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.09 (s, 1H), 8.03 (d, ^3J=7.8 Hz, 1H), 7.94 (d, ^3J=7.9 Hz, 1H), 7.72 (t, ^3J=7.8 Hz, 1H), 7.68 (s, 1H), 6.20 (d, ^3J=5.5 Hz, 1H), 5.03 (d, ^2J=12.4 Hz, 1H), 4.87 (d, ^3J=4.7 Hz, 1H), 4.82 (d, ^2J=12.4 Hz, 1H), 4.75 (m, 1H), 4.45 (d, ^3J=7.0 Hz, 1H), 4.33 (s, 1H), 4.32 (d, ^3J=8.4 Hz, 1H), 4.21 (m, 2H), 4.03 (dq, ^3J=12.5 Hz, 6.5 Hz, 1H), 3.68 (m, 2H), 3.55 (d, ^3J=7.0 Hz, 1H), 3.50 (m, 1H), 3.45 (d, ^3J=8.3 Hz, 1H), 3.21 (s, 3H), 3.10 (s, 3H), 3.05 (s, 3H), 2.93 (m, 1H), 2.69 (m, 2H), 2.39 (d, ^2J=12.2 Hz, 1H), 2.27 (d, ^2J=15.0 Hz, 1H), 2.21 (s, 3H), 2.20 (m, 1H), 2.14 (m, 1H), 1.96 (m, 1H), 1.92 (m, 1H), 1.79 (m, 1H), 1.62 (m, 2H), 1.54 (dd, ^2J=15.1 Hz, ^3J=4.9 Hz, 1H), 1.39 (m, 1H), 1.33 (m, 1H), 1.20 (s, 3H), 1.16 (d, ^3J=6.2 Hz, 3H), 1.14 (d, ^3J=6.3 Hz, 3H), 1.13 (s, 3H), 1.10 (d, ^3J=7.6 Hz, 3H), 1.02 (s, 3H), 1.00 (d, ^3J=7.7 Hz, 3H), 0.95 (d, ^3J=6.6 Hz, 3H), 0.87 (d, ^3J=6.8 Hz, 3H), 0.80 (t, ^3J=7.5 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 177.2, 138.2, 137.1, 130.1, 130.1, 118.2, 113.8, 112.8, 101.0, 94.4, 82.8, 77.1, 77.1, 76.3, 75.0, 73.6, 72.8, 72.5, 70.2, 69.9, 68.7, 66.1, 65.8, 64.7, 61.5, 49.8, 49.0, 47.6, 44.6, 41.8, 41.2, 35.7, 34.5, 32.3, 27.4, 26.1, 22.2, 21.1, 21.1, 20.9, 18.6, 17.7, 14.7, 11.0, 9.0, 6.7; FT-IR (KBr pellet): a broad band at 3393 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 2232 cm^{-1} ν(C≡N); 1727 cm^{-1} ν(C_1=O)$_{lactone}$, 1460 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O), 1065 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 943.4769; Elemental analysis $C_{46}H_{78}BrN_3O_{12}$:

calculated: C=58.46%; H=8.32%; Br=8.46%; N=4.45%; measured: C=58.48%; H=8.31%; Br=8.46%; N=4.46%; HPLC: R_t = 1.96 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

General procedure for the synthesis of new *N*-alkylammonium clarithromycin bromide derivatives 4a-4e, 4i together with the analytical data.

Clarithromycin (**CLA**) was purchased from Carbosynth (>99%). **CLA** (100.0 mg, 0.13 mmol) was dissolved in 5 ml anhydrous ACN, respective mixtures were prepared with each of following compounds taken separately (0.52 mmol): allyl bromide, crotyl bromide, 3,3-dimethylallyl bromide, 3-bromo-1-phenyl-1-propene, propargyl bromide and 3-(bromomethyl)thiophene. The mixtures were stirred at room temperature for 2-16 hours. Next, the reaction mixture was evaporated to dryness, dissolved in 2ml CH_2Cl_2 and the obtained solution was added by dropwise into the 50 ml hexane. Obtained precipitate was filtered and dried under the vacuum. All ^{1}H and ^{13}C NMR data of **4a-4e**, **4i** are collected in **Tables 7S - 8S**.

4a Yield: 88%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 6.08 (ddt, ^3J=17.0 Hz, 10.2 Hz, 7.0 Hz, 1H), 5.97 (d, ^3J=5.4 Hz, 1H), 5.64 (dd, ^3J=10.2 Hz, 1.8 Hz, 1H), 5.60 (dd, ^3J=16.9 Hz, 1.7 Hz, 1H), 5.06 (dd, ^3J=11.2 Hz, 2.4 Hz, 1H), 4.80 (d, ^3J=5.0 Hz, 1H), 4.45 (d, ^3J=6.9 Hz, 1H), 4.42 (d, ^3J=7.4 Hz, 1H), 4.30 (dd, ^2J=12.8 Hz, ^3J=7.4 Hz, 1H), 4.17 (dd, ^2J=12.7 Hz, ^3J=6.9 Hz, 1H), 4.15 (s, 1H), 3.97 (dq, ^3J=9.2 Hz, 6.1 Hz, 1H), 3.71 (m, 1H), 3.65 (m, 1H), 3.64 (m, 1H), 3.64 (d, ^3J=4.6 Hz, 1H), 3.60 (dd, ^3J=9.6 Hz, 1.4 Hz, 1H), 3.56 (m, 1H), 3.46 (ddd, ^2J=12.0 Hz, ^3J=10.3 Hz, 4.1 Hz, 1H), 3.22 (s, 3H), 3.06 (s, 3H), 3.03 (s, 3H), 2.97 (s, 3H), 2.96 (m, 1H), 2.94 (dd, ^3J=9.6 Hz, 7.3 Hz, 1H), 2.81 (dq, ^3J=9.6 Hz, 7.3 Hz, 1H), 2.58 (ddq, ^3J=10.2 Hz, 7.2 Hz, 3.5 Hz, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.05 (m, 1H), 1.89 (t, ^3J=7.3 Hz, 1H), 1.82 (ddd, ^2J=14.2 Hz, ^3J=7.5 Hz, 2.3 Hz, 1H), 1.75 (dd, ^2J=14.8 Hz, ^3J=10.1 Hz, 1H), 1.58 (m, 1H), 1.56 (m, 1H), 1.49 (dd, ^2J=14.8 Hz, ^3J=3.3 Hz, 1H), 1.38 (m, 1H), 1.30 (s, 3H), 1.17 (d, ^3J=6.2 Hz, 3H), 1.15 (d, ^3J=6.1 Hz, 3H), 1.15 (s, 3H), 1.13 (d, ^3J=7.3 Hz, 3H), 1.05 (d, ^3J=7.0 Hz, 3H), 1.03 (d, ^3J=7.1 Hz, 1H), 1.02 (s, 3H), 1.01 (d, ^3J=7.0 Hz, 3H), 0.75 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 218.3, 175.1, 127.7, 126.4, 100.9, 95.7, 79.7, 77.8, 77.0, 77.0, 76.0, 74.2, 72.6, 70.7, 69.7, 68.9, 66.7, 65.7, 65.1, 50.2, 49.5, 48.9, 48.1, 44.4, 43.2, 38.5, 38.4, 38.3, 34.6, 32.2, 21.1, 20.8, 20.7, 20.0, 18.8, 17.7, 17.1, 15.7, 11.8, 10.5, 9.2; FT-IR (KBr pellet): a broad band at 3407 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 1730 cm^{-1} ν(C_1=O)$_{lactone}$, 1690 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O); 1065 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 867.4344; Elemental analysis $C_{41}H_{74}BrNO_{13}$: calculated: C=56.67%; H=8.58%; Br=9.20%; N=1.61%; measured: C=56.66%; H=8.59%; Br=9.21%; N=1.59%; HPLC: R_t = 1.65 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 99%;

4b Yield: 94%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 6.02 (m, 1H), 5.94 (d, ^3J=5.4 Hz, 1H), 5.68 (m, 1H), 4.80 (d, ^3J=5.0 Hz, 1H), 5.06 (dd, ^3J=11.1 Hz, 2.4 Hz, 1H), 4.44 (d, ^3J=7.4 Hz, 1H), 4.43 (d, ^3J=6.7 Hz, 1H), 4.28 (dd, ^2J=12.9 Hz, ^3J=7.8 Hz, 1H), 4.14 (s, 1H), 4.07 (dd, ^2J=12.6 Hz, ^3J=7.1 Hz, 1H), 3.97 (dq, ^3J=9.2 Hz, 6.1 Hz, 1H), 3.72 (m, 1H), 3.64 (m, 1H), 3.60 (d, ^3J=9.6 Hz, 1H), 3.60 (m, 1H), 3.58 (m, 1H), 3.53 (m, 1H), 3.43 (ddd, ^3J=12.4 Hz, 10.2 Hz, 4.1 Hz, 1H), 3.23 (s, 3H), 3.03 (s, 3H), 2.97 (s, 3H), 2.96 (s, 3H), 2.95 (m, 1H), 2.93 (m, 1H), 2.80 (m, 1H), 2.57 (m, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.03 (m, 1H), 1.88 (t, ^3J=7.5 Hz, 1H), 1.82 (m, 1H), 1.77 (m, 1H), 1.77 (d, ^3J=5.9 Hz, 1H), 1.73 (m, 1H), 1.55 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.30 (s, 3H), 1.16 (d, ^3J=6.1 Hz, 3H), 1.15 (s, 3H), 1.14 (d, ^3J=7.0 Hz, 3H), 1.13 (d, ^3J=7.0 Hz, 3H), 1.05 (d, ^3J=7.2 Hz, 3H), 1.03 (d, ^3J=7.0 Hz, 1H), 1.02 (s, 3H), 1.01 (d, ^3J=7.0 Hz, 3H), 0.75 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 218.3, 175.1, 139.6, 119.1, 100.9, 95.6, 79.7, 77.8, 77.0, 76.9, 76.0, 74.2, 72.6, 70.7, 68.9, 68.9, 66.6, 65.7, 65.1, 50.2, 49.2, 48.9, 47.7, 44.4, 43.2, 38.4, 38.4, 38.3, 34.6, 32.2, 21.0, 20.8, 20.8, 20.0, 18.8, 18.1, 17.8, 17.1, 15.7, 11.8, 10.5, 9.2; FT-IR (KBr pellet): a broad band at 3415 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 1733 cm^{-1} ν(C_1=O)$_{lactone}$, 1689 cm^{-1} ν(C=C), 1169 cm^{-1} ν(C-O), 1075 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 881.4513; Elemental analysis $C_{42}H_{76}BrNO_{13}$: calculated: C=57.13%; H=8.68%; Br=9.05%; N=1.59%; measured: C=57.14%; H=8.70%; Br=9.03%; N=1.61%; HPLC: R_t = 1.65 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

4c Yield: 91%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 5.99 (d, ^3J=5.2 Hz, 1H), 5.42 (m, 1H), 5.06 (dd, ^3J=11.1 Hz, 2.4 Hz, 1H),4.80 (d, ^3J=5.1 Hz, 1H), 4.47 (d, ^3J=7.3 Hz, 1H), 4.44 (d, ^3J=7.0 Hz, 1H), 4.25 (dd, ^2J=13.2 Hz, ^3J=8.2 Hz, 1H), 4.18 (dd, ^2J=13.1 Hz, ^3J=7.8 Hz, 1H), 4.15 (s, 1H), 3.97 (dq, ^3J=9.4 Hz, 6.1 Hz, 1H), 3.73 (m, 1H), 3.64 (d, ^3J=9.4 Hz, 1H), 3.63 (m, 1H), 3.60 (m, 1H), 3.54 (m, 1H), 3.45 (ddd, ^3J=12.3 Hz, 10.5 Hz, 4.1 Hz, 1H), 3.22 (s, 3H), 3.02 (s, 3H), 2.97 (s, 3H), 2.96 (s, 3H), 2.94 (m, 1H), 2.93 (m, 1H), 2.80 (m, 1H), 2.57 (m, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.03 (m, 1H), 1.88 (t, ^3J=7.3 Hz, 1H), 1.82 (s, 3H), 1.81 (m, 1H), 1.75 (s, 3H), 1.73 (m, 1H), 1.60 (m, 1H), 1.56 (m, 1H), 1.49 (m, 1H), 1.38 (dq, ^3J=11.2 Hz, 7.2 Hz, 1H), 1.30 (s, 3H), 1.17 (d, ^3J=6.1 Hz, 3H), 1.15 (s, 3H), 1.14 (d, ^3J=7.1 Hz, 3H), 1.14 (d, ^3J=7.1 Hz, 3H), 1.05 (d, ^3J=7.1 Hz, 1H), 1.03 (d, ^3J=6.8 Hz, 3H), 1.02 (s, 3H), 1.01 (d, ^3J=7.2 Hz, 3H), 0.75 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 218.3, 175.1, 145.8, 112.2, 101.0, 95.6, 79.7, 77.8, 77.0, 76.9, 76.0, 74.2, 72.6, 70.8, 68.9, 68.9, 65.8, 65.1, 62.7, 50.2, 49.0, 48.8, 47.1, 44.3, 43.2, 38.5, 38.4, 38.3, 34.6, 32.3, 26.1, 21.1, 20.8, 20.8, 20.0, 18.8, 18.4, 17.8, 17.1, 15.7, 11.8, 10.5, 9.1; FT-IR (KBr pellet): a broad band at 3413 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 1730 cm^{-1} ν(C_1=O)$_{lactone}$, 1689 cm^{-1} ν(C=C), 1170 cm^{-1} ν(C-O), 1076 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 895.4657; Elemental analysis $C_{43}H_{78}BrNO_{13}$: calculated: C=57.58%; H=8.76%; Br=8.91%; N=1.56%; measured: C=57.60%; H=8.75%; Br=8.92%; N=1.57%; HPLC: R_t = 1.65 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

4d Yield: 93%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.55 (m, 2H), 7.40 (m, 2H), 7.36 (m, 1H), 6.87 (d, ^3J=15.6 Hz, 1H), 6.49 (dt, ^3J=15.3 Hz, 7.4 Hz, 1H), 6.01 (d, ^3J=5.0 Hz, 1H), 5.07 (dd, ^3J=11.1 Hz, 2.4 Hz, 1H), 4.79 (d, ^3J=5.0 Hz, 1H), 4.56 (dd, ^2J=12.9 Hz, ^3J=7.5 Hz, 1H), 4.47 (d, ^3J=7.6 Hz, 1H), 4.37 (d, ^3J=7.6 Hz, 1H), 4.31 (dd, ^2J=12.9 Hz, ^3J=7.2 Hz, 1H), 4.15 (s, 1H), 3.96 (dq, ^3J=9.3 Hz, 6.1 Hz, 1H), 3.72 (m, 1H), 3.64 (m, 1H), 3.64 (d, ^3J=6.3 Hz, 1H), 3.63 (m, 1H), 3.60 (m, 1H), 3.56 (m, 1H), 3.50 (m, 1H), 3.11 (s, 3H), 3.10 (s, 3H), 3.08 (s, 3H), 2.97 (s, 3H), 2.95 (m, 1H), 2.92 (dd, ^3J=9.6 Hz, 7.6 Hz, 1H), 2.81 (dq, ^3J=9.3 Hz, 7.2 Hz, 1H), 2.58 (m, 1H), 2.25 (d, ^2J=15.1 Hz, 1H), 2.07 (m, 1H), 1.89 (t, ^3J=7.3 Hz, 1H), 1.82 (m, 1H), 1.76 (dd, ^2J=14.7 Hz, ^3J=10.0 Hz, 1H), 1.60 (m, 1H), 1.57 (m, 1H), 1.50 (m, 1H), 1.39 (dq, ^3J=11.1 Hz, 7.2 Hz, 1H), 1.31 (s, 3H), 1.16 (d, ^3J=6.0 Hz, 3H), 1.15 (d, ^3J=6.0 Hz, 3H), 1.13 (d, ^3J=7.2 Hz, 3H), 1.09 (s, 3H), 1.06 (d, ^3J=6.0 Hz, 1H), 1.04 (d, ^3J=6.8 Hz, 3H), 1.03 (s, 3H), 0.75 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 218.3, 175.1, 140.8, 135.3, 128.9, 128.7, 128.7, 127.1, 127.1, 117.0, 101.0, 95.6, 79.7, 77.8, 77.0, 76.9, 76.0, 74.2, 72.5, 70.8, 69.0, 69.0, 67.2, 65.8, 65.1, 50.2, 49.6, 48.8, 47.8, 44.4, 43.2, 38.5, 38.4, 38.3, 34.6, 32.2, 21.0, 20.8, 20.6, 20.1, 18.8, 17.8, 17.1, 15.7, 11.8, 10.5, 9.2; FT-IR (KBr pellet): a broad band at 3430 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 1732 cm^{-1} ν(C_1=O)$_{lactone}$, 1689 cm^{-1} ν(C=C), 1460 cm^{-1} ν(C=C), 1170 cm^{-1} ν(C-O), 1076 cm^{-1} ν(C-O); HR-MALDI-TOF [M+H]$^+$ = 943.4657; Elemental analysis $C_{47}H_{78}BrNO_{13}$: calculated: C=59.73%; H=8.32%; Br=8.46%; N=1.48%; measured: C=59.74%; H=8.30%; Br=8.44%; N=1.49%; HPLC: R_t = 1.66 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 99%;

4e Yield: 94%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 6.06 (d, ^3J=5.2 Hz, 1H), 5.22 (dd, ^2J=16.0 Hz, ^4J=2.3 Hz, 1H), 5.06 (dd, ^3J=11.1 Hz, 2.4 Hz, 1H), 4.80 (d, ^3J=4.7 Hz, 1H), 4.78 (dd, ^2J=17.2 Hz, ^4J=2.8 Hz, 1H), 4.54 (d, ^3J=7.0 Hz, 1H), 4.48 (d, ^3J=7.0 Hz, 1H), 4.09 (t, ^4J=2.4 Hz, 1H), 3.97 (dq, ^3J=12.1 Hz, 6.0 Hz, 1H), 4.14 (s, 1H), 3.79 (m, 1H), 3.64 (m, 1H), 3.64 (d, ^3J=7.5 Hz, 1H), 3.67 (m, 1H), 3.60 (m, 1H), 3.53 (m, 1H), 3.49 (m, 1H), 3.24 (s, 3H), 3.15 (s, 3H), 3.10 (s, 3H), 2.96 (s, 3H), 2.95 (m, 1H), 2.93 (m, 1H), 2.81 (m, 1H), 2.56 (ddq, ^3J=10.3 Hz, 6.9 Hz, 3.2 Hz, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.08 (m, 1H), 1.87 (q, ^3J=7.4 Hz, 1H), 1.81 (m, 1H), 1.74 (dd, ^2J=14.9 Hz, ^3J=10.4 Hz, 1H), 1.59 (m, 1H), 1.54 (dd, ^2J=15.2 Hz, ^3J=5.2 Hz, 1H), 1.49 (dd, ^2J=14.8 Hz, ^3J=3.1 Hz, 1H), 1.38 (m, 1H), 1.29 (s, 3H), 1.16 (d, ^3J=6.1 Hz, 3H), 1.15 (d, ^3J=7.0 Hz, 3H), 1.14 (s, 3H),

1.13 (d, ^3J=7.2 Hz, 3H), 1.05 (d, ^3J=7.0 Hz, 3H), 1.03 (d, ^3J=7.0 Hz, 1H), 1.02 (s, 3H), 1.01 (d, ^3J=8.0 Hz, 3H), 0.75 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 218.3, 175.1, 100.7, 95.6, 83.3, 79.7, 77.7, 77.0, 76.7, 76.0, 74.2, 73.0, 72.6, 70.7, 69.5, 68.9, 65.7, 65.0, 56.2, 50.2, 50.0, 49.0, 47.6, 44.3, 43.3, 38.4, 38.3, 38.2, 34.6, 32.3, 21.1, 20.8, 20.7, 20.0, 18.9, 17.8, 17.1, 15.7, 11.8, 10.5, 9.2; FT-IR (KBr pellet): a broad band at 3429 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2125 cm^{-1} ν(C≡C), 1732 cm^{-1} ν(C_1=O)$_{lactone}$, 1689 cm^{-1} ν(C=C), 1170 cm^{-1} ν(C-O), 1076 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 865.4187; Elemental analysis $C_{41}H_{72}BrNO_{13}$: calculated: C=56.80%; H=8.37%; Br=9.22%; N=1.62%; measured: C=56.79%; H=8.35%; Br=9.21%; N=1.62%; HPLC: R_t = 1.65 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

4i Yield: 89%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.85 (dd, ^3J=2.8 Hz, ^4J=1.3 Hz, 1H), 7.71 (dd, ^3J=5.0 Hz, 2.9 Hz, 1H), 7.29 (dd, ^3J=4.9 Hz, ^4J=1.3 Hz, 1H), 6.18 (d, ^3J=5.4 Hz, 1H), 5.07 (dd, ^3J=11.1 Hz, 2.4 Hz, 1H), 4.98 (d, ^2J=12.6 Hz, 1H), 4.80 (d, ^3J=5.0 Hz, 1H), 4.73 (d, ^3J=12.5 Hz, 1H), 4.43 (d, ^3J=7.0 Hz, 2H), 4.15 (s, 1H), 3.97 (m, 1H), 3.68 (m, 1H), 3.66 (m, 3H), 3.62 (m, 1H), 3.62 (d, ^3J=10.1 Hz, 1H), 3.44 (ddd, ^3J=12.4 Hz, 10.9 Hz, 3.8 Hz, 1H), 3.20 (s, 3H), 3.06 (s, 3H), 2.99 (s, 3H), 2.98 (s, 3H), 2.95 (m, 1H), 2.93 (dd, ^3J=9.4 Hz, 7.2 Hz, 1H), 2.83 (m, 1H), 2.59 (ddq, ^3J=10.9 Hz, 7.2 Hz, 3.4 Hz, 1H), 2.29 (d, ^2J=15.0 Hz, 1H), 2.06 (m, 1H), 1.90 (t, ^3J=7.5 Hz, 1H), 1.83 (m, 1H), 1.78 (dd, ^2J=14.6 Hz, ^3J=10.1 Hz, 1H), 1.60 (d, ^3J=12.4 Hz, 1H), 1.54 (m, 1H), 1.52 (m, 1H), 1.39 (dq, ^3J=11.1 Hz, 7.1 Hz, 1H), 1.31 (s, 3H), 1.16 (d, ^3J=6.1 Hz, 3H), 1.14 (d, ^3J=7.2 Hz, 3H), 1.14 (d, ^3J=7.2 Hz, 3H), 1.13 (s, 3H), 1.07 (d, ^3J=6.9 Hz, 1H), 1.06 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 1.04 (d, ^3J=6.0 Hz, 3H), 0.76 (t, ^3J=7.4 Hz, 3H); ^{13}C NMR (500 MHz; DMSO-d_6): δ 218.3, 175.2, 131.9, 130.7, 128.9, 127.5, 101.0, 95.7, 79.4, 77.8, 77.0, 76.9, 76.0, 74.2, 72.6, 70.8, 69.0, 68.8, 65.9, 65.1, 62.2, 50.3, 49.6, 49.2, 47.5, 44.4, 43.2, 38.5, 38.5, 38.3, 34.6, 32.1, 21.1, 20.7, 20.7, 20.1, 18.9, 17.8, 17.1, 15.7, 11.8, 10.5, 9.1; FT-IR (KBr pellet): a broad band at 3428 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 1732 cm^{-1} ν(C_1=O)$_{lactone}$, 1689 cm^{-1} ν(C=C), 1170 cm^{-1} ν(C-O); 1076 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 923.4064; Elemental analysis $C_{43}H_{74}BrNO_{13}S$: calculated: C=55.83%; H=8.06%; Br=8.64%; N=1.52%; S=3.47%; measured C=55.81%; H=8.05%; Br=8.65%; N=1.52%; S=3.46%; HPLC: R_t = 1.66 min (H_2O:CH_3CN:0.1% NH_4OH 10:65:25), purity: 98%;

General procedure for the synthesis of new carbonate-triazole azithromycins 5x$_1$-5x$_{18}$ together with the analytical data.

Azithromycin (**AZM**) was purchased from Carbosynth (>98%). **AZM** (100.0 mg, 0.13 mmol) was dissolved in 5 ml acetone and 2 ml 0.25M HCl. The mixture was stirred at 25°C for 24 hours and after that 2 ml saturated $NaHCO_3$ was added to stop the reactions. Organic layer was extracted three time with 50 ml of saturated $NaHCO_3$. The separated organic layers were evaporated. Next, the obtained solid state product was dissolved in 5 ml ACN and catalytic amount of propargyl chloroformate was added. The reaction was stirred by 30 min, then evaporated, dissolved in 50 ml CH_2Cl_2 and then organic layer was extracted three time with 50 ml of saturated $NaHCO_3$. Obtained precipitate was dissolved in a 4 ml mixture of THF/MeOH (3:1) and respective mixtures were prepared with each of following compounds taken separately (1.2 molar equiv.): azidocyclohexane, (azidomethyl)cyclohexane, azidocycloheptane, (azidomethyl)benzene, 1-(azidomethyl)-4-methylbenzene, 4-(azidomethyl)benzonitrile, 1-(azidomethyl)-4-nitrobenzene, 1-(azidomethyl)-4-fluorobenzene, 1-(azidomethyl)-4-chlorobenzene, 1-(azidomethyl)-4-bromobenzene, 2-(3-azidopropyl)isoindoline-1,3-dione, 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl azide, 1-azido-1-deoxy-β-D-galactopyranoside tetraacetate, 2,3,4,6-tetra-*O*-acetyl-1-azido-1-deoxy-α-D-galactopyranosyl cyanide, 2-acetamido-2-deoxy-β-D-glucopyranosyl azide 3,4,6-triacetate, 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl azide and 3′-azido-3′-deoxythymidine. Then, to each mixture, ~20 mg (1.2 molar equiv.) of CH3COOCu (I) and ~40 mg (1.8 molar equiv.) of ascorbic acid were added. The mixtures were stirred at room temperature for 1-8 hours and evaporated after that. Next, 25 ml of EtOAc was added and extracted three times with 25 ml of saturated $NaHCO_3$. The separated organic layers was evaporated, given the products **5x$_1$-5x$_{18}$**. Next, the obtained product were purified by column chromatography with silica gel (25 cm × 1 cm, silica gel 60, 0.040-0.063 mm/230-400 mesh ASTM, Fluka) with dichloromethane/methanol (from 60:1 to 10:1) as an eluent. All ^{1}H and ^{13}C NMR data of **5x$_1$-5x$_{18}$** are collected in **Tables 9S - 12S**.

5x$_1$ Yield*: 35%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.64 (s, 1H), 5.28 (d, ^2J=12.6 Hz, 1H), 5.26 (d, ^2J=12.7 Hz, 1H), 4.75 (d, ^3J=7.6 Hz, 1H), 4.70 (dd, ^3J=10.8 Hz, 1.2 Hz, 1H), 4.57 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 4.43 (tt, ^3J=11.7 Hz, 3.8 Hz, 1H), 3.64 (d, ^3J=10.6 Hz, 1H), 3.62 (m, 1H), 3.57 (d, ^3J=1.5 Hz, 1H), 3.51 (ddq, ^3J=12.4 Hz, 6.3 Hz, 1.8 Hz, 1H), 2.75 (m, 1H), 2.72 (m, 1H), 2.62 (dq, ^3J=10.6 Hz, 6.8 Hz, 1H), 2.49 (dd, ^2J=12.3 Hz, ^3J=3.0 Hz, 1H), 2.36 (s, 3H), 2.26 (s, 6H), 2.23 (m, 1H), 2.04 (t, ^2J=11.9 Hz, 1H), 2.19 (m, 2H), 1.93 (m, 2H), 1.90 (m, 1H), 1.89 (m, 1H), 1.78 (m, 1H), 1.77 (m, 1H), 1.72 (m, 2H), 1.56 (d, ^2J=13.9 Hz, 1H), 1.52 (m, 1H), 1.47 (m, 2H), 1.35 (m, 1H), 1.30 (m, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.25 (m, 1H), 1.24 (s, 3H), 1.22 (d, ^3J=6.2 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.92 (d, ^3J=7.0 Hz, 3H), 0.88 (t, ^3J=7.3 Hz, 3H), 0.71 (d, ^3J=7.4 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.6, 142.2, 121.5, 100.5, 88.1, 78.9, 77.7, 76.2, 75.9, 74.4, 73.2, 71.2, 68.9, 63.4, 62.7, 61.2, 60.2, 44.2, 41.7, 40.8, 40.8, 36.9, 35.8, 33.7, 33.6, 30.6, 26.4, 26.2, 25.2, 25.2, 25.2, 21.4, 21.1, 21.0, 16.2, 16.2, 11.0, 7.7, 7.1; FT-IR (KBr pellet): a broad band at 3429 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 1751 cm^{-1} ν(C_9=O), 1713 cm^{-1} ν(C_1=O)$_{lactone}$, 1263 cm^{-1} ν(C-O), 1170 cm^{-1} ν(C-O), 1112 cm^{-1} ν(C-O) 1045 cm^{-1}, ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 797.5224; Elemental analysis $C_{40}H_{71}N_5O_{11}$: calculated: C=62.20%; H=8.97%; N=8.78%; measured: C=62.23%; H=8.99%; N=8.79%; HPLC: R_t = 6.91 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_2$ Yield*: 37%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.59 (s, 1H), 5.31 (d, ^2J=12.7 Hz, 1H), 5.24 (d, ^2J=12.7 Hz, 1H), 4.75 (d, ^3J=7.6 Hz, 1H), 4.68 (dd, ^3J=10.6 Hz, 1.1 Hz, 1H), 4.57 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 4.17 (d, ^2J=2.8 Hz, 1H), 4.15 (d, ^2J=2.6 Hz, 1H), 3.66 (d, ^3J=11.4 Hz, 1H), 3.64 (m, 1H), 3.59 (d, ^3J=1.6 Hz, 1H), 3.51 (ddq, ^3J=12.3 Hz, 6.1 Hz, 1.6 Hz, 1H), 2.76 (m, 1H), 2.72 (d, ^3J=6.5 Hz 1H), 2.62 (dq, ^3J=10.6 Hz, 6.9 Hz, 1H), 2.50 (dd, ^2J=12.2 Hz, ^3J=2.9 Hz, 1H), 2.37 (s, 3H), 2.27 (m, 1H), 2.25 (s, 6H), 2.06 (t, ^2J=12.4 Hz, 1H), 1.94 (m, 1H), 1.90 (m, 1H), 1.87 (m, 1H), 1.72 (m, 3H), 1.62 (m, 1H), 1.60 (m, 2H), 1.53 (m, 1H), 1.50 (m, 2H), 1.35 (m, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.25 (m, 1H), 1.24 (s, 3H), 1.24 (m, 2H), 1.23 (d, ^3J=6.2 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.99 (m, 2H), 0.92 (d, ^3J=7.0 Hz, 3H), 0.88 (t, ^3J=7.4 Hz, 3H), 0.77 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.6, 142.6, 124.1, 100.5, 87.9, 78.9, 77.9, 76.3, 76.1, 74.4, 73.2, 71.2, 69.0, 63.5, 62.7, 61.2, 56.7, 44.2, 41.7, 40.8, 40.8, 37.0, 35.9, 38.9, 30.7, 30.6, 30.6, 26.5, 26.2, 26.2, 25.6, 25.6, 21.5, 21.2, 21.0, 16.3, 16.2, 11.1, 7.8, 7.2; FT-IR (KBr pellet): a broad band at 3426 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2636 cm^{-1} ν(O_6-H), 1751 cm^{-1} ν(C_9=O), 1712 cm^{-1} ν(C_1=O)$_{lactone}$, 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1045 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 811.5324; Elemental analysis $C_{41}H_{73}N_5O_{11}$: calculated: C=60.64%; H=9.06%; N=8.62%; measured: C=60.67%; H=9.04%; N=8.63%; HPLC: R_t = 7.12 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_3$ Yield*: 39%; ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.63 (s, 1H), 5.29 (d, ^2J=12.8 Hz, 1H), 5.25 (d, ^2J=12.7 Hz, 1H), 4.75 (d, ^3J=7.6 Hz, 1H), 4.70 (d, ^3J=10.4 Hz, 1H), 4.65 (m, 1H), 4.57 (dd, ^3J=10.3 Hz, 7.7 Hz, 1H), 3.65 (d, ^3J=8.8 Hz, 1H), 3.62 (m, 1H), 3.58 (d, ^3J=1.2 Hz, 1H), 3.51 (m, 1H), 2.76 (m, 1H), 2.73 (m, 1H), 2.62 (dq, ^3J=10.5 Hz, 6.8 Hz, 1H), 2.50 (dd, ^2J=12.2 Hz, ^3J=2.9 Hz, 1H), 2.37 (s, 3H), 2.26 (s, 6H), 2.24 (m, 1H), 2.05 (t, ^2J=11.6 Hz, 1H), 2.17 (m, 2H), 1.96 (m, 2H), 1.90 (m, 1H), 1.89 (m, 1H), 1.83 (m, 2H), 1.72 (m, 1H), 1.71 (m, 1H), 1.64 (m, 1H), 1.59 (m, 2H), 1.56 (d, ^2J=14.1 Hz, 1H), 1.52 (m, 1H), 1.35 (m, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.25 (m, 1H), 1.24 (s, 3H), 1.23 (d, ^3J=6.1 Hz, 3H), 1.12 (d, ^3J=6.8 Hz, 3H), 1.06 (s, 3H), 0.92 (d, ^3J=6.9 Hz, 3H), 0.88 (t, ^3J=7.3 Hz, 3H), 0.74 (d, ^3J=7.4 Hz, 3H); ^{13}C NMR (600 MHz; $CDCl_3$): δ 177.6, 154.6, 142.4, 121.5, 100.6, 88.2, 79.0, 77.8, 76.2, 76.0, 74.4, 73.2, 71.3, 69.0, 63.5, 62.7, 62.7, 61.2, 44.2, 41.7, 40.8, 40.8, 37.0, 35.9, 35.8, 35.8, 30.6, 27.9, 27.9, 26.4, 26.2, 24.4, 24.4, 21.5, 21.2, 21.0, 16.3, 16.2, 11.1, 7.7,

7.2; FT-IR (KBr pellet): a broad band at 3427 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2637 cm^{-1} $\nu(O_6\text{-}H)$, 1752 cm^{-1} $\nu(C_{9'}\text{=}O)$, 1713 cm^{-1} $\nu(C_1\text{=}O)_{lactone}$, 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1112 cm^{-1} ν(C-O), 1045 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 811.5321; Elemental analysis $C_{41}H_{73}N_5O_{11}$: calculated: C=60.64%; H=9.06%; N=8.62%; measured: C=60.65%; H=9.07%; N=8.60%; HPLC: R_t = 7.72 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_4$ Yield*: 50%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.54 (s, 1H), 7.37 (m, 2H), 7.36 (m, 1H), 7.26 (m, 2H), 5.54 (d, ^2J=14.8 Hz, 1H), 5.48 (d, ^2J=14.8 Hz, 1H), 5.29 (d, ^2J=12.8 Hz, 1H), 5.20 (d, ^2J=12.8 Hz, 1H), 4.73 (d, ^3J=7.6 Hz, 1H), 4.68 (dd, ^3J=10.8 Hz, 1.4 Hz, 1H), 4.54 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 3.65 (d, ^3J=9.6 Hz, 1H), 3.63 (m, 1H), 3.58 (d, ^3J=1.7 Hz, 1H), 3.49 (ddq, ^3J=12.3 Hz, 6.1 Hz, 1.8 Hz, 1H), 2.74 (m, 1H), 2.70 (m, 1H), 2.62 (dq, ^3J=10.6 Hz, 6.9 Hz, 1H), 2.49 (dd, ^2J=12.3 Hz, ^3J=2.9 Hz, 1H), 2.36 (s, 3H), 2.24 (m, 1H), 2.17 (s, 6H), 2.06 (t, ^2J=11.8 Hz, 1H), 1.90 (m, 1H), 1.87 (m, 1H), 1.70 (ddd, ^2J=12.5 Hz, ^3J=4.0 Hz, 1.5 Hz, 1H), 1.55 (d, ^2J=14.2 Hz, 1H), 1.54 (m, 1H), 1.35 (d, ^2J=12.4 Hz, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.27 (m, 1H), 1.23 (s, 3H), 1.22 (d, ^3J=6.1 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.91 (d, ^3J=6.9 Hz, 3H), 0.89 (t, ^3J=7.4 Hz, 3H), 0.78 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.3, 143.3, 134.5, 129.3, 129.3, 129.0, 128.2, 128.2, 123.5, 100.4, 87.9, 78.9, 77.9, 76.3, 76.1, 74.4, 73.2, 71.2, 69.0, 63.5, 62.6, 61.1, 54.4, 44.2, 41.7, 40.7, 40.7, 37.0, 35.9, 30.7, 26.5, 26.1, 21.5, 21.1, 21.0, 16.3, 16.2, 11.1, 7.7, 7.2; FT-IR (KBr pellet): a broad band at 3434 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2635 cm^{-1} $\nu(O_6\text{-}H)$, 1752 cm^{-1} $\nu(C_{9'}\text{=}O)$, 1721 cm^{-1} $\nu(C_1\text{=}O)_{lactone}$, 1498 cm^{-1} ν(C=C), 1455 cm^{-1} ν(C=C), 1283 cm^{-1} ν(C-O), 1170 cm^{-1} ν(C-O), 1112 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 805.4840; Elemental analysis $C_{41}H_{67}N_5O_{11}$: calculated: C=61.10%; H=8.38%; N=8.69%; measured: C=61.11%; H=8.40%; N=8.71%; HPLC: R_t = 6.50 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_5$ Yield*: 48%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.64 (d, ^3J=8.1 Hz, 2H), 7.61 (s, 1H), 7.37 (d, ^3J=8.0 Hz, 2H), 5.62 (d, ^2J=15.3 Hz, 1H), 5.56 (d, ^2J=15.2 Hz, 1H), 5.32 (d, ^2J=12.8 Hz, 1H), 5.20 (d, ^2J=12.8 Hz, 1H), 4.74 (d, ^3J=7.6 Hz, 1H), 4.70 (d, ^3J=10.6 Hz, 1H), 4.55 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 3.66 (d, ^3J=10.9 Hz, 1H), 3.63 (m, 1H), 3.59 (d, ^3J=1.4 Hz, 1H), 3.49 (ddq, ^3J=12.0 Hz, 6.3 Hz, 1.6 Hz, 1H), 2.74 (m, 1H), 2.70 (m, 1H), 2.63 (dq, ^3J=10.5 Hz, 6.8 Hz, 1H), 2.51 (dd, ^2J=12.1 Hz, ^3J=2.8 Hz, 1H), 2.36 (s, 3H), 2.25 (s, 3H), 2.24 (m, 1H), 2.16 (s, 6H), 2.06 (t, ^2J=11.8 Hz, 1H), 1.90 (m, 2H), 1.71 (m, 1H), 1.56 (d, ^2J=14.3 Hz, 1H), 1.52 (m, 1H), 1.35 (d, ^2J=12.5 Hz, 1H), 1.26 (d, ^3J=6.8 Hz, 3H), 1.26 (m, 1H), 1.23 (s, 3H), 1.22 (d, ^3J=6.3 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.91 (d, ^3J=7.0 Hz, 3H), 0.88 (t, ^3J=7.5 Hz, 3H), 0.80 (d, ^3J=7.4 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.5, 143.1, 139.0, 131.4, 129.9, 129.9, 128.3, 128.3, 123.4, 100.3, 87.8, 78.8, 77.8, 76.2, 76.2, 74.4, 73.2, 71.2, 69.0, 63.4, 62.6, 61.1, 54.2, 44.1, 41.6, 40.7, 40.7, 37.0, 35.9, 30.6, 26.4, 26.2, 21.5, 21.3, 21.1, 21.0, 16.3, 16.2, 11.1, 7.7, 7.3; FT-IR (KBr pellet): a broad band at 3429 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2637 cm^{-1} $\nu(O_6\text{-}H)$, 1752 cm^{-1} $\nu(C_{9'}\text{=}O)$, 1713 cm^{-1} $\nu(C_1\text{=}O)_{lactone}$, 1455 cm^{-1} ν(C=C), 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O); 1113 cm^{-1} ν(C-O), 1078 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 819.4998; Elemental analysis $C_{42}H_{69}N_5O_{11}$: calculated: C=61.52%; H=8.48%; N=8.54%; measured: C=61.51%; H=8.49%; N=8.56%; HPLC: R_t = 6.70 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_6$ Yield*: 42%; ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.68 (d, ^3J=8.3 Hz, 2H), 7.64 (s, 1H), 7.34 (d, ^3J=8.1 Hz, 2H), 5.61 (d, ^2J=15.3 Hz, 1H), 5.57 (d, ^2J=15.5 Hz, 1H), 5.33 (d, ^2J=12.8 Hz, 1H), 5.20 (d, ^2J=12.9 Hz, 1H), 4.74 (d, ^3J=7.6 Hz, 1H), 4.69 (dd, ^3J=10.6 Hz, 1.6 Hz, 1H), 4.55 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 3.66 (d, ^3J=10.3 Hz, 1H), 3.63 (m, 1H), 3.60 (d, ^3J=1.5 Hz, 1H), 3.49 (ddq, ^3J=12.1 Hz, 6.1 Hz, 1.7 Hz, 1H), 2.74 (m, 1H), 2.71 (ddd, ^2J=12.3 Hz, ^3J=10.7 Hz, 4.5 Hz, 1H), 2.63 (dq, ^3J=10.5 Hz, 6.9 Hz, 1H), 2.51 (dd, ^2J=12.2 Hz, ^3J=2.8 Hz, 1H), 2.37 (s, 3H), 2.25 (m, 1H), 2.18 (s, 6H), 2.07 (t, ^2J=11.8 Hz, 1H), 1.90 (m, 1H), 1.90 (ddq, ^2J=15.0 Hz, ^3J=7.4 Hz, 1.7 Hz, 1H), 1.72 (ddd, ^2J=12.6 Hz, ^3J=4.0 Hz, 1.3 Hz, 1H), 1.56 (d, ^2J=14.6 Hz, 1H), 1.52 (m, 1H), 1.34 (d, ^2J=12.4 Hz, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.26 (m, 1H), 1.24 (s, 3H), 1.22 (d, ^3J=6.1 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.92 (d, ^3J=7.0 Hz, 3H), 0.89 (t, ^3J=7.3 Hz, 3H), 0.81 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (600 MHz; $CDCl_3$): δ 177.5, 154.4, 143.6, 139.6, 132.9, 132.9, 128.4, 128.4, 123.8, 118.0, 113.0, 100.1, 87.4, 78.6, 77.8, 76.2, 76.0, 74.3, 73.1, 71.0, 68.8, 63.3, 62.5, 60.9, 53.4, 44.0, 41.5, 40.6, 40.6, 36.9, 35.9, 30.3, 26.3, 26.1, 21.4, 21.0, 20.9, 16.2, 16.1, 11.0, 7.6, 7.2; FT-IR (KBr pellet): a broad band at 3447 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2637 cm^{-1} $\nu(O_6\text{-}H)$, 2230 cm^{-1} ν(C≡N); 1752 cm^{-1} $\nu(C_{9'}\text{=}O)$, 1713 cm^{-1} $\nu(C_1\text{=}O)_{lactone}$, 1455 ν(C=C), 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1113 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 830.4791; Elemental analysis $C_{42}H_{66}N_6O_{11}$: calculated: C=60.70%; H=8.01%; N=10.11%; measured: C=60.74%; H=8.03%; N=10.12%; HPLC: R_t = 7.40 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_7$ Yield*: 49%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.23 (d, ^3J=8.8 Hz, 2H), 7.65 (s, 1H), 7.40 (d, ^3J=8.8 Hz, 2H), 5.66 (d, ^2J=15.5 Hz, 1H), 5.61 (d, ^2J=15.6 Hz, 1H), 5.32 (d, ^2J=12.8 Hz, 1H), 5.20 (d, ^2J=12.8 Hz, 1H), 4.73 (d, ^3J=7.6 Hz, 1H), 4.68 (d, ^3J=9.9 Hz, 1H), 4.54 (dd, ^3J=10.4 Hz, 7.7 Hz, 1H), 3.65 (d, ^3J=10.4 Hz, 1H), 3.61 (m, 1H), 3.58 (d, ^3J=1.2 Hz, 1H), 3.49 (ddq, ^3J=12.0 Hz, 6.2 Hz, 1.7 Hz, 1H), 2.71 (dd, ^3J=10.5 Hz, 4.2 Hz, 1H), 2.67 (m, 1H), 2.62 (dq, ^3J=10.6 Hz, 6.8 Hz, 1H), 2.49 (dd, ^2J=12.0 Hz, ^3J=2.5 Hz, 1H), 2.35 (s, 3H), 2.25 (m, 1H), 2.17 (s, 6H), 2.05 (t, ^2J=11.7 Hz, 1H), 1.89 (m, 2H), 1.70 (ddd, ^2J=12.7 Hz, ^3J=4.3 Hz, 1.4 Hz, 1H), 1.55 (d, ^2J=14.1 Hz, 1H), 1.51 (m, 1H), 1.35 (d, ^2J=12.5 Hz, 1H), 1.25 (d, ^3J=6.8 Hz, 3H), 1.25 (m, 1H), 1.22 (s, 3H), 1.21 (d, ^3J=6.1 Hz, 3H), 1.11 (d, ^3J=6.8 Hz, 3H), 1.05 (s, 3H), 0.90 (d, ^3J=7.0 Hz, 3H), 0.87 (t, ^3J=7.4 Hz, 3H), 0.79 (d, ^3J=7.4 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.5, 148.2, 143.8, 141.5, 128.7, 128.7, 124.5, 124.5, 123.9, 100.3, 87.7, 78.8, 77.9, 76.3, 76.0, 74.4, 73.2, 71.2, 69.0, 63.4, 62.7, 61.0, 53.3, 44.2, 41.7, 40.8, 40.8, 37.0, 35.9, 30.4, 26.5, 26.3, 21.5, 21.2, 21.0, 16.3, 16.2, 11.1, 7.7, 7.3; FT-IR (KBr pellet): a broad band at 3430 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2636 cm^{-1} $\nu(O_6\text{-}H)$, 1752 cm^{-1} $\nu(C_{9'}\text{=}O)$, 1714 cm^{-1} $\nu(C_1\text{=}O)_{lactone}$, 1523 cm^{-1} $\nu(NO_2)$; 1457 cm^{-1} ν(C=C), 1347 cm^{-1} $\nu(NO_2)$; 1262 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1113 cm^{-1} ν(C-O); 1045 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 850.4690; Elemental analysis $C_{41}H_{66}N_6O_{13}$: calculated: C=57.87%; H=7.82%; N=9.88%; measured: C=57.90%; H=7.74%; N=9.90%; HPLC: R_t = 7.80 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_8$ Yield*: 43%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56 (s, 1H), 7.25 (d, ^3J=8.6 Hz, 2H), 7.07 (d, ^3J=8.6 Hz, 2H), 5.52 (d, ^2J=14.9 Hz, 1H), 5.46 (d, ^2J=14.9 Hz, 1H), 5.30 (d, ^2J=12.8 Hz, 1H), 5.20 (d, ^2J=12.8 Hz, 1H), 4.73 (d, ^3J=7.6 Hz, 1H), 4.69 (dd, ^3J=10.8 Hz, 1.4 Hz, 1H), 4.54 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 3.66 (d, ^3J=8.4 Hz, 1H), 3.63 (m, 1H), 3.58 (d, ^3J=1.6 Hz, 1H), 3.50 (ddq, ^3J=12.3 Hz, 6.0 Hz, 1.8 Hz, 1H), 2.74 (m, 1H), 2.71 (m, 1H), 2.69 (dd, ^2J=10.8 Hz, ^3J=1.4 Hz, 1H), 2.62 (dq, ^3J=10.5 Hz, 6.8 Hz, 1H), 2.50 (dd, ^2J=12.2 Hz, ^3J=3.0 Hz, 1H), 2.36 (s, 3H), 2.24 (m, 1H), 2.17 (s, 6H), 2.06 (t, ^2J=11.9 Hz, 1H), 1.90 (ddq, ^2J=15.1 Hz, ^3J=7.6 Hz, 1.9 Hz, 1H), 1.90 (m, 1H), 1.71 (ddd, ^2J=12.7 Hz, ^3J=4.1 Hz, 1.6 Hz, 1H), 1.55 (d, ^2J=14.9 Hz, 1H), 1.53 (m, 1H), 1.32 (m, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.26 (m, 1H), 1.23 (s, 3H), 1.22 (d, ^3J=6.2 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.91 (d, ^3J=6.8 Hz, 3H), 0.89 (t, ^3J=7.4 Hz, 3H), 0.78 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 163.0 (d, ^1J =248.6), 154.5, 143.4, 123.4, 130.4 (d, ^4J =3.3), 130.1 (d, ^3J =8.4), 130.1 (d, ^3J =8.4), 116.3 (d, ^2J =21.8), 116.3 (d, ^2J =21.8), 100.3, 87.8, 78.8, 77.8, 76.2, 76.0, 74.4, 73.2, 71.2, 69.0, 63.4, 62.6, 61.1, 53.6, 44.1, 41.7, 40.7, 40.7, 37.0, 35.9, 30.5, 26.4, 26.2, 21.5, 21.1, 21.0, 16.3, 16.2, 11.1, 7.8, 7.3; FT-IR (KBr pellet): a broad band at 3434 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2638 cm^{-1} $\nu(O_6\text{-}H)$, 1752 cm^{-1} $\nu(C_{9'}\text{=}O)$, 1713 cm^{-1} $\nu(C_1\text{=}O)_{lactone}$, 1457 cm^{-1} ν(C=C), 1262 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1113 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O), 1005 cm^{-1} ν(C-F); HR-MALDI-TOF $[M+H]^+$ = 823.4747; Elemental analysis $C_{41}H_{66}FN_5O_{11}$: calculated: C=59.76%; H=8.07%; F=2.31%; N=8.50%; measured: C=59.80%; H=8.09%; F=2.32%; N=8.51%; HPLC: R_t = 8.40 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_9$ Yield*: 50%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.63 (d, ^3J=8.1 Hz, 2H), 7.59 (s, 1H), 7.36 (d, ^3J=8.0 Hz, 2H), 5.61 (d, ^2J=15.3 Hz, 1H), 5.55 (d,

^2J=15.2 Hz, 1H), 5.31 (d, ^2J=12.8 Hz, 1H), 5.19 (d, ^2J=12.8 Hz, 1H), 4.73 (d, ^3J=7.6 Hz, 1H), 4.68 (dd, ^3J=10.7 Hz, 1.7 Hz, 1H), 4.53 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 3.64 (d, ^3J=10.6 Hz, 1H), 3.61 (m, 1H), 3.57 (d, ^3J=1.4 Hz, 1H), 3.48 (ddq, ^3J=12.2 Hz, 6.0 Hz, 1.8 Hz, 1H), 2.72 (m, 1H), 2.69 m, 1H), 2.61 (dq, ^3J=10.5 Hz, 6.8 Hz, 1H), 2.57 (d, ^3J=1.4 Hz, 1H), 2.48 (dd, ^2J=12.2 Hz, ^3J=2.8 Hz, 1H), 2.35 (s, 3H), 2.23 (m, 1H), 2.14 (s, 6H), 2.05 (t, ^2J=11.9 Hz, 1H), 1.90 (m, 1H), 1.88 (ddq, ^2J=14.8 Hz, ^3J=7.4 Hz, 1.7 Hz, 1H), 1.69 (ddd, ^2J=12.9 Hz, ^3J=4.4 Hz, 1.7 Hz, 1H), 1.55 (d, ^2J=14.1 Hz, 1H), 1.50 (m, 1H), 1.35 (m, 1H), 1.27 (m, 1H), 1.25 (d, ^3J=6.8 Hz, 3H), 1.22 (s, 3H), 1.21 (d, ^3J=6.3 Hz, 3H), 1.10 (d, ^3J=6.9 Hz, 3H), 1.05 (s, 3H), 0.90 (d, ^3J=7.0 Hz, 3H), 0.87 (t, ^3J=7.4 Hz, 3H), 0.78 (d, ^3J=7.4 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.5, 143.6, 138.5, 131.3 (q, ^2J =32.8), 128.3, 128.3, 126.3 (d, ^3J =3.8), 126.3 (d, ^3J =3.8), 123.7, 123.4 (q, ^1J =235.5), 100.3, 87.7, 78.8, 77.9, 76.3, 76.0, 74.4, 73.2, 71.2, 69.0, 63.4, 62.6, 61.0, 53.7, 44.1, 41.7, 40.7, 40.7, 37.0, 35.9, 30.4, 26.5, 26.2, 21.5, 21.1, 21.0, 16.2, 16.2, 11.1, 7.7, 7.3; FT-IR (KBr pellet): a broad band at 3434 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 2635 cm^{-1} ν(O_6-H), 1753 cm^{-1} ν($C_{9'}$=O), 1714 cm^{-1} ν(C_1=O)$_{lactone}$, 1457 cm^{-1} ν(C=C), 1326 cm^{-1} ν(CF_3), 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1113 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 873.4711; Elemental analysis $C_{42}H_{66}F_3N_5O_{11}$: calculated: C=57.72%; H=7.61%; F=6.52%; N=8.01%; measured: C=57.74%; H=7.60%; F=6.51%; N=5.16%; HPLC: R_t = 9.40 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{10}$ Yield*: 42%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56 (s, 1H), 7.35 (d, ^3J=8.5 Hz, 2H), 7.20 (d, ^3J=8.5 Hz, 2H), 5.51 (d, ^2J=15.0 Hz, 1H), 5.46 (d, ^2J=14.9 Hz, 1H), 5.30 (d, ^2J=12.8 Hz, 1H), 5.20 (d, ^2J=12.8 Hz, 1H), 4.73 (d, ^3J=7.6 Hz, 1H), 4.69 (dd, ^3J=10.7 Hz, 1.3 Hz, 1H), 4.54 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 3.66 (d, ^3J=8.7 Hz, 1H), 3.63 (d, ^3J=5.7 Hz, 1H), 3.58 (d, ^3J=1.7 Hz, 1H), 3.49 (ddq, ^3J=12.3 Hz, 6.1 Hz, 1.7 Hz, 1H), 2.73 (m, 2H), 2.62 (dq, ^3J=10.5 Hz, 6.8 Hz, 1H), 2.50 (dd, ^2J=12.2 Hz, ^3J=2.9 Hz, 1H), 2.36 (s, 3H), 2.25 (m, 1H), 2.18 (s, 6H), 2.06 (t, ^2J=11.8 Hz, 1H), 1.90 (m, 2H), 1.71 (ddd, ^2J=12.9 Hz, ^3J=4.3 Hz, 1.6 Hz, 1H), 1.56 (d, ^2J=14.4 Hz, 1H), 1.53 (m, 1H), 1.34 (m, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.26 (m, 1H), 1.23 (s, 3H), 1.22 (d, ^3J=6.2 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.91 (d, ^3J=6.8 Hz, 3H), 0.89 (t, ^3J=7.4 Hz, 3H), 0.78 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.5, 143.4, 135.1, 133.0, 129.5, 129.5, 129.5, 129.5, 123.5, 100.3, 87.8, 78.8, 77.9, 76.3, 76.0, 74.4, 73.2, 71.2, 69.0, 63.4, 62.7, 61.1, 53.6, 44.2, 41.7, 40.7, 40.7, 37.0, 35.9, 30.5, 26.5, 26.2, 21.5, 21.2, 21.0, 16.3, 16.2, 11.1, 7.8, 7.3; FT-IR (KBr pellet): a broad band at 3430 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 1752 cm^{-1} ν($C_{9'}$=O), 1714 cm^{-1} ν(C_1=O)$_{lactone}$, 1494 cm^{-1} ν(C=C), 1457 cm^{-1} ν(C=C), 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1113 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O), 794 cm^{-1} ν(C-Cl); HR-MALDI-TOF $[M+H]^+$ = 839.4450; Elemental analysis $C_{41}H_{66}ClN_5O_{11}$: calculated: C=58.59%; H=7.92%; Cl=4.22%; N=8.33%; measured: C=58.62%; H=7.89%; Cl=4.21%; N=8.32%; HPLC: R_t = 8.30 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{11}$ Yield*: 33%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56 (s, 1H), 7.51 (d, ^3J=8.4 Hz, 2H), 7.14 (d, ^3J=8.4 Hz, 2H), 5.51 (d, ^2J=15.0 Hz, 1H), 5.46 (d, ^2J=14.9 Hz, 1H), 5.30 (d, ^2J=12.8 Hz, 1H), 5.20 (d, ^2J=12.8 Hz, 1H), 4.73 (d, ^3J=7.6 Hz, 1H), 4.69 (dd, ^3J=10.7 Hz, 1.3 Hz, 1H), 4.54 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 3.66 (d, ^3J=7.1 Hz, 1H), 3.63 (d, ^3J=5.7 Hz, 1H), 3.59 (d, ^3J=1.6 Hz, 1H), 3.49 (ddq, ^3J=12.3 Hz, 6.1 Hz, 1.7 Hz, 1H), 2.73 (m, 2H), 2.63 (m, 1H), 2.50 (dd, ^2J=12.2 Hz, ^3J=2.9 Hz, 1H), 2.36 (s, 3H), 2.25 (m, 1H), 2.18 (s, 6H), 2.06 (t, ^2J=11.8 Hz, 1H), 1.90 (m, 2H), 1.71 (ddd, ^2J=12.9 Hz, ^3J=4.3 Hz, 1.6 Hz, 1H), 1.56 (d, ^2J=14.4 Hz, 1H), 1.53 (m, 1H), 1.34 (m, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.26 (m, 1H), 1.23 (s, 3H), 1.22 (d, ^3J=6.2 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.06 (s, 3H), 0.91 (d, ^3J=6.8 Hz, 3H), 0.89 (t, ^3J=7.4 Hz, 3H), 0.78 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 154.5, 143.4, 133.5, 132.5, 132.5, 129.8, 129.8, 123.5, 123.2, 100.3, 87.8, 78.8, 77.9, 76.3, 76.0, 74.4, 73.2, 71.2, 69.0, 63.4, 62.7, 61.1, 53.6, 44.2, 41.7, 40.7, 40.7, 37.0, 35.9, 30.5, 26.5, 26.2, 21.5, 21.2, 21.0, 16.3, 16.2, 11.1, 7.8, 7.3; FT-IR (KBr pellet): a broad band at 3444 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 1752 cm^{-1} ν($C_{9'}$=O), 1713 cm^{-1} ν(C_1=O)$_{lactone}$, 1490 cm^{-1} ν(C=C), 1457 cm^{-1} ν(C=C), 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1113 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O), 794 cm^{-1} ν(C-Br); HR-MALDI-TOF $[M+H]^+$ = 883.3942; Elemental analysis $C_{41}H_{66}BrN_5O_{11}$: calculated: C=55.65%; H=7.52%; Br=9.03%; N=7.91%; measured: C=55.65%; H=7.53%; Br=9.00%; N=7.90; HPLC: R_t = 8.42 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{12}$ Yield*: 31%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.86 (dd, ^3J=5.5 Hz, ^4J=3.0 Hz, 2H), 7.82 (s, 1H), 7.75 (dd, ^3J=5.5 Hz, ^4J=3.0 Hz, 2H), 5.29 (d, ^2J=12.7 Hz, 1H), 5.22 (d, ^2J=12.6 Hz, 1H), 4.74 (d, ^3J=7.6 Hz, 1H), 4.67 (d, ^3J=10.0 Hz, 1H), 4.57 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 4.40 (m, 2H), 3.76 (m, 2H), 3.66 (m, 1H), 3.62 (m, 1H), 3.58 (d, ^3J=6.0 Hz, 1H), 3.50 (m, 1H), 2.76 (m, 1H), 2.72 m, 1H), 2.63 (m, 1H), 2.50 (m, 1H), 2.36 (s, 3H), 2.33 (m, 2H), 2.25 (m, 1H), 2.25 (s, 6H), 2.07 (m, 1H), 1.90 (m, 1H), 1.88 (m, 1H), 1.72 (m, 2H), 1.56 (d, ^2J=13.9 Hz, 1H), 1.51 (m, 1H), 1.34 (m, 1H), 1.26 (d, ^3J=6.9 Hz, 3H), 1.28 (m, 1H), 1.24 (s, 3H), 1.22 (d, ^3J=6.2 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.05 (s, 3H), 0.91 (d, ^3J=6.9 Hz, 3H), 0.86 (t, ^3J=7.3 Hz, 3H), 0.78 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 168.4, 168.4, 154.5, 142.7, 134.4, 134.4, 132.0, 132.0, 124.2, 123.6, 123.6, 100.5, 87.9, 78.9, 77.9, 76.3, 76.0, 74.4, 73.3, 71.2, 69.0, 63.5, 62.7, 61.1, 48.1, 44.2, 41.7, 40.9, 40.9, 37.0, 36.0, 35.1, 30.7, 29.7, 26.5, 26.3, 21.5, 21.2, 21.0, 16.3, 16.2, 11.1, 7.8, 7.2; FT-IR (KBr pellet): a broad band at 3440 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2'}$-H)+ν($O_{4''}$-H), 2636 cm^{-1} ν(O_6-H), 1768 cm^{-1} ν(C=O); 1752 cm^{-1} ν($C_{9'}$=O), 1713 cm^{-1} ν(C_1=O)$_{lactone}$, 1490 cm^{-1} ν(C=C), 1457 cm^{-1} ν(C=C), 1263 cm^{-1} ν(C-O), 1169 cm^{-1} ν(C-O), 1113 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 902.5012; Elemental analysis $C_{45}H_{70}N_6O_{13}$: calculated: C=59.85%; H=7.81%; N=9.31%; measured: C=52.82%; H=7.82%; N=9.33%; HPLC: R_t = 9.58 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{13}$ Yield*: 36%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.84 (s, 1H), 5.77 (d, ^3J=8.8 Hz, 1H), 5.41 (t, ^3J=9.2 Hz, 1H), 5.37 (t, ^3J=8.7 Hz, 1H), 5.37 (d, ^2J=13.6 Hz, 1H), 5.19 (d, ^2J=12.8 Hz, 1H), 5.13 (ddd, ^3J=10.3 Hz, 9.2 Hz, 5.7 Hz, 1H), 4.73 (d, ^3J=7.6 Hz, 1H), 4.67 (dd, ^3J=10.8 Hz, 1.4 Hz, 1H), 4.55 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 4.29 (d, ^2J=11.6 Hz, ^3J=5.6 Hz, 1H), 3.66 (d, ^3J=10.5 Hz, 1H), 3.63 (m, 1H), 3.59 (d, ^2J=11.7 Hz, ^3J=10.3 Hz, 1H), 3.58 (d, ^3J=1.4 Hz, 1H), 3.49 (m, 1H), 2.74 (m, 1H), 2.70 (m, 1H), 2.64 (m, 1H), 2.48 (dd, ^2J=12.2 Hz, ^3J=3.0 Hz, 1H), 2.35 (s, 3H), 2.26 (m, 1H), 2.23 (s, 6H), 2.07 (s, 3H), 2.06 (m, 1H), 2.05 (s, 3H), 1.90 (m, 1H), 1.88 (s, 3H), 1.88 (m, 1H), 1.71 (ddd, ^2J=12.9 Hz, ^3J=4.9 Hz, 1.7 Hz, 1H), 1.56 (d, ^2J=14.4 Hz, 1H), 1.51 (m, 1H), 1.34 (m, 1H), 1.30 (m, 1H), 1.26 (d, ^3J=6.8 Hz, 3H), 1.23 (s, 3H), 1.22 (d, ^3J=6.1 Hz, 3H), 1.11 (d, ^3J=6.9 Hz, 3H), 1.05 (s, 3H), 0.91 (d, ^3J=7.0 Hz, 3H), 0.87 (t, ^3J=7.3 Hz, 3H), 0.81 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 170.0, 169.8, 160.0, 154.4, 143.4, 122.1, 100.3, 87.7, 86.5, 78.9, 77.9, 76.4, 76.1, 74.4, 73.2, 72.1, 71.2, 70.6, 69.0, 68.5, 65.7, 63.5, 62.6, 60.8, 44.2, 41.7, 40.8, 40.8, 37.0, 35.9, 30.6, 26.5, 26.3, 21.5, 21.2, 21.0, 20.7, 20.7, 20.3, 16.3, 16.2, 11.1, 7.8, 7.3; FT-IR (KBr pellet): a broad band at 3444 cm^{-1} ν(O_{11}-H)+ν(O_{12}-H)+ν($O_{2''}$-H)+ν($O_{4''}$-H), 2637 cm^{-1} ν(O_6-H), 1750 cm^{-1} ν($C_{9'}$=O)+ν(C_1=O)$_{lactone}$+ν(C=O)$_{acetyl}$, 1457 cm^{-1} ν(C=C), 1247 cm^{-1} ν((C=O)-O), 1169 cm^{-1} ν(C-O), 1098 cm^{-1} ν(C-O), 1046 cm^{-1} ν(C-O); HR-MALDI-TOF $[M+H]^+$ = 973.5107; Elemental analysis $C_{45}H_{75}N_5O_{18}$: calculated: C=55.49%; H=7.76%; N=7.19%; measured: C=55.50%; H=7.78%; N=7.20%; HPLC: R_t = 5.35 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{14}$ Yield*: 31%; ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.95 (s, 1H), 5.87 (d, ^3J=9.3 Hz, 1H), 5.56 (dd, ^3J=3.2 Hz, 0.7 Hz, 1H), 5.52 (dd, ^3J=10.2 Hz, 9.4 Hz, 1H), 5.38 (d, ^2J=12.8 Hz, 1H), 5.26 (dd, ^3J=10.3 Hz, 3.4 Hz, 1H), 5.16 (d, ^2J=12.3 Hz, 1H), 4.76 (d, ^3J=7.6 Hz, 1H), 4.71 (dd, ^3J=10.8 Hz, 1.3 Hz, 1H), 4.57 (dd, ^3J=10.5 Hz, 7.7 Hz, 1H), 4.24 (ddd, ^3J=7.0 Hz, 6.1 Hz, 1.1 Hz, 1H), 4.19 (dd, ^2J=11.4 Hz, ^3J=6.0 Hz, 1H), 4.11 (dd, ^2J=11.4 Hz, ^3J=6.9 Hz, 1H), 3.67 (d, ^3J=10.7 Hz, 1H), 3.64 (m, 1H), 3.61 (d, ^3J=1.6 Hz, 1H), 3.49 (ddq, ^3J=12.3 Hz, 6.1 Hz, 1.6 Hz, 1H), 2.74 (m, 1H), 2.71 (m, 1H), 2.65 (dq, ^3J=10.5 Hz, 6.9 Hz, 1H), 2.50 (dd, ^2J=12.3 Hz, ^3J=2.9 Hz, 1H), 2.37 (s, 3H), 2.27 (m, 1H), 2.23 (s, 6H), 2.22 (s, 3H), 2.09 (t, ^2J=12.4 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.92 (m, 1H), 1.90 (m, 1H), 1.89 (s, 3H), 1.72 (ddd, ^2J=12.5 Hz, ^3J=4.2 Hz, 1.6 Hz, 1H), 1.59 (d, ^2J=14.2 Hz, 1H), 1.53 (ddd, ^2J=14.2 Hz, ^3J=10.9 Hz, 7.1 Hz, 1H), 1.35 (m, 1H), 1.30 (m, 1H), 1.27 (d, ^3J=6.8 Hz, 3H), 1.25 (s, 3H), 1.23 (d, ^3J=6.1 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.07 (s, 3H), 0.93 (d, ^3J=7.0 Hz, 3H), 0.87 (t, ^3J=7.5 Hz, 3H), 0.87 (d, ^3J=7.6 Hz, 3H); ^{13}C NMR (600 MHz; $CDCl_3$): δ 177.6, 170.4, 170.0, 169.1, 166.9, 154.6, 143.4, 122.3, 100.2,

87.5, 86.5, 78.8, 77.8, 76.4, 76.0, 74.3, 74.2, 73.3, 71.2, 70.9, 69.0, 68.1, 67.0, 63.5, 62.6, 61.3, 60.9, 44.1, 41.7, 40.7, 40.7, 37.0, 35.9, 30.5, 26.5, 26.2, 21.5, 21.1, 21.0, 20.7, 20.7, 20.6, 20.3, 16.2, 16.2, 11.1, 7.7, 7.3; FT-IR (KBr pellet): a broad band at 3491 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2637 cm^{-1} $\nu(O_6\text{-}H)$, 1756 cm^{-1} $\nu(C_{9'}{=}O)+\nu(C_1{=}O)_{lactone}+\nu(C{=}O)_{acetyl}$, 1457 cm^{-1} $\nu(C{=}C)$, 1255 cm^{-1} $\nu((C{=}O)\text{-}O)$, 1169 cm^{-1} $\nu(C\text{-}O)$, 1098 cm^{-1} $\nu(C\text{-}O)$, 1046 cm^{-1} $\nu(C\text{-}O)$; HR-MALDI-TOF $[M+H]^+$ = 1045.5318; Elemental analysis $C_{48}H_{79}N_5O_{20}$: calculated: C=55.11%; H=7.61%; N=6.69%; measured: C=55.10%; H=7.63%; N=6.70%; HPLC: R_t = 5.25 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{15}$ Yield*: 23%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.99 (s, 1H), 5.75 (d, ^3J=10.7 Hz, 1H), 5.64 (dd, ^3J=3.2 Hz, 1.3 Hz, 1H), 5.43 (dd, ^3J=10.7 Hz, 3.2 Hz, 1H), 5.37 (d, ^2J=13.1 Hz, 1H), 5.20 (d, ^2J=13.0 Hz, 1H), 4.76 (d, ^3J=7.6 Hz, 1H), 4.70 (m, 1H), 4.63 (dd, ^3J=6.1 Hz, 1.0 Hz, 1H), 4.56 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 4.28 (dd, ^2J=11.6 Hz, ^3J=6.7 Hz, 1H), 4.17 (dd, ^2J=11.6 Hz, ^3J=6.7 Hz, 1H), 3.67 (d, ^3J=10.5 Hz, 1H), 3.63 (m, 1H), 3.60 (d, ^3J=1.7 Hz, 1H), 3.49 (ddq, ^3J=12.0 Hz, 6.1 Hz, 2.2 Hz, 1H), 2.74 (m, 1H), 2.72 (m, 1H), 2.63 (m, 1H), 2.50 (dd, ^2J=12.2 Hz, ^3J=2.8 Hz, 1H), 2.36 (s, 3H), 2.27 (m, 1H), 2.23 (s, 6H), 2.21 (s, 3H), 2.07 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.98 (m, 1H), 1.89 (m, 1H), 1.72 (ddd, ^2J=12.8 Hz, ^3J=4.3 Hz, 1.7 Hz, 1H), 1.57 (d, ^2J=14.0 Hz, 1H), 1.51 (m, 1H), 1.34 (m, 1H), 1.30 (m, 1H), 1.26 (d, ^3J=6.8 Hz, 3H), 1.24 (s, 3H), 1.23 (d, ^3J=6.1 Hz, 3H), 1.11 (d, ^3J=6.9 Hz, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.92 (d, ^3J=7.0 Hz, 3H), 0.87 (t, ^3J=7.4 Hz, 3H), 0.84 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.6, 170.2, 169.7, 169.5, 168.4, 154.5, 144.1, 122.2, 111.1, 100.1, 87.5, 86.8, 78.8, 77.9, 76.5, 76.1, 74.4, 74.3, 73.2, 71.1, 69.3, 69.0, 68.4, 66.2, 63.5, 62.6, 60.7, 60.7, 44.1, 41.6, 40.8, 40.8, 37.0, 35.9, 30.3, 26.5, 26.2, 21.5, 21.2, 21.0, 20.7, 20.7, 20.5, 20.4, 16.3, 16.2, 11.1, 7.8, 7.3; FT-IR (KBr pellet): a broad band at 3485 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2635 cm^{-1} $\nu(O_6\text{-}H)$, 2248 cm^{-1} $\nu(C{\equiv}N)$; 1756 cm^{-1} $\nu(C_{9'}{=}O)+\nu(C_1{=}O)_{lactone}+\nu(C{=}O)_{acetyl}$, 1456 $cm^{-1}\nu(C{=}C)$, 1258 cm^{-1} $\nu((C{=}O)\text{-}O)$, 1169 cm^{-1} $\nu(C\text{-}O)$, 1098 cm^{-1} $\nu(C\text{-}O)$, 1046 cm^{-1} $\nu(C\text{-}O)$; HR-MALDI-TOF $[M+H]^+$ = 1070.5271; Elemental analysis $C_{49}H_{78}N_6O_{20}$: calculated: C=54.94%; H=7.34%; N=7.85%; measured: C=54.95%; H=7.32%; N=7.86%; HPLC: R_t = 5.21 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{16}$ Yield*: 15%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.95 (s, 1H), 6.17 (d, ^3J=10.0 Hz, 1H), 5.86 (d, ^3J=9.4 Hz, 1H), 5.38 (dd, ^3J=10.2 Hz, 9.4 Hz, 1H), 5.38 (d, ^2J=12.8 Hz, 1H), 5.38 (dd, ^3J=3.2 Hz, 0.7 Hz, 1H), 5.16 (d, ^2J=12.3 Hz, 1H), 4.76 (d, ^3J=7.6 Hz, 1H), 4.71 (dd, ^3J=10.8 Hz, 1.3 Hz, 1H), 4.56 (dd, ^3J=10.5 Hz, 7.7 Hz, 1H), 4.53 (dd, ^3J=10.8 Hz, 3.4 Hz, 1H), 4.21 (dd, ^2J=11.4 Hz, ^3J=6.3 Hz, 1H), 4.14 (dd, ^2J=11.4 Hz, ^3J=6.8 Hz, 1H), 4.09 (m, 1H), 3.66 (d, ^3J=10.7 Hz, 1H), 3.63 (m, 1H), 3.60 (d, ^3J=1.6 Hz, 1H), 3.49 (ddq, ^3J=12.3 Hz, 6.1 Hz, 1.7 Hz, 1H), 2.74 (m, 1H), 2.71 (m, 1H), 2.66 (dq, ^3J=10.4 Hz, 6.9 Hz, 1H), 2.50 (dd, ^2J=12.2 Hz, ^3J=2.9 Hz, 1H), 2.37 (s, 3H), 2.27 (m, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 2.22 (s, 3H), 2.09 (t, ^2J=12.2 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.92 (m, 1H), 1.90 (m, 1H), 1.72 (s, 3H), 1.72 (ddd, ^2J=12.6 Hz, ^3J=4.2 Hz, 1.7 Hz, 1H), 1.59 (d, ^2J=14.2 Hz, 1H), 1.54 (ddd, ^2J=14.2 Hz, ^3J=10.9 Hz, 7.1 Hz, 1H), 1.35 (m, 1H), 1.30 (m, 1H), 1.26 (d, ^3J=6.8 Hz, 3H), 1.25 (s, 3H), 1.23 (d, ^3J=6.1 Hz, 3H), 1.12 (d, ^3J=6.9 Hz, 3H), 1.07 (s, 3H), 0.93 (d, ^3J=7.0 Hz, 3H), 0.86 (t, ^3J=7.5 Hz, 3H), 0.86 (d, ^3J=7.6 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.7, 170.4, 170.0, 169.4, 166.9, 154.4, 143.1, 123.0, 100.1, 87.5, 86.2, 78.8, 77.8, 76.2, 75.7, 74.4, 74.0, 73.4, 71.2, 71.1, 68.9, 68.0, 63.5, 62.6, 61.5, 60.8, 55.4, 44.2, 41.6, 40.8, 40.8, 37.0, 36.0, 30.7, 26.5, 26.3, 21.5, 21.1, 21.0, 20.7, 20.7, 20.6, 20.3, 16.3, 16.3, 11.1, 7.6, 7.3; FT-IR (KBr pellet): a broad band at 3434 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2636 cm^{-1} $\nu(O_6\text{-}H)$, 1752 cm^{-1} $\nu(C_{9'}{=}O)+\nu(C_1{=}O)_{lactone}+\nu(C{=}O)_{acetyl}$, 1676 cm^{-1} $\nu(C{=}O)_{amide}$, 1546 cm^{-1} $\delta(C\text{-}N)_{amide}$, 1457 $\nu(C{=}C)$, 1258 cm^{-1} $\nu((C{=}O)\text{-}O)$, 1169 cm^{-1} $\nu(C\text{-}O)$, 1098 cm^{-1} $\nu(C\text{-}O)$, 1046 cm^{-1} $\nu(C\text{-}O)$; HR-MALDI-TOF $[M+H]^+$ = 1044.5478; Elemental analysis $C_{48}H_{80}N_6O_{19}$: calculated: C=55.16%; H=7.71%; N=8.04%; measured: C=55.18%; H=7.72%; N=8.03%; HPLC: R_t = 5.16 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{17}$ Yield*: 25%; ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.90 (s, 1H), 7.32 (m, 6H), 7.29 (m, 6H), 7.19 (dd, ^3J=7.4 Hz, 1.8 Hz, 2H), 7.14 (dd, ^3J=7.4 Hz, 1.8 Hz, 1H), 5.94 (d, ^3J=9.8 Hz, 1H), 5.86 (d, ^3J=9.4 Hz, 1H), 5.31 (d, ^2J=12.6 Hz, 1H), 5.13 (d, ^2J=12.6 Hz, 1H), 4.87 (d, ^2J=11.6 Hz, 1H), 4.84 (d, ^2J=10.8 Hz, 1H), 4.76 (d, ^3J=7.6 Hz, 1H), 4.72 (d, ^3J=9.8 Hz, 1H), 4.70 (d, ^2J=11.6 Hz, 1H), 4.61 (d, ^2J=10.8 Hz, 1H), 4.56 (dd, ^3J=10.5 Hz, 7.6 Hz, 1H), 4.55 (d, ^2J=12.1 Hz, 1H), 4.47 (d, ^2J=12.1 Hz, 1H), 4.27 (dd, ^3J=10.0 Hz, 9.8 Hz, 1H), 4.03 (dd, ^3J=10.1 Hz, 8.6 Hz, 1H), 3.84 (dd, ^3J=9.7 Hz, 8.5 Hz, 1H), 3.79 (ddd, ^3J=9.8 Hz, 3.6 Hz, 1.8 Hz, 1H), 3.75 (dd, ^2J=10.9 Hz, ^3J=3.8 Hz, 1H), 3.70 (dd, ^2J=11.0 Hz, ^3J=1.5 Hz, 1H), 3.66 (m, 1H), 3.65 (m, 1H), 3.62 (m, 1H), 3.47 (ddq, ^3J=12.3 Hz, 6.1 Hz, 1.7 Hz, 1H), 2.76 (m, 1H), 2.71 (m, 1H), 2.66 (dq, ^3J=10.4 Hz, 6.8 Hz, 1H), 2.49 (d, ^2J=10.9 Hz, 1H), 2.36 (s, 3H), 2.25 (m, 1H), 2.20 (s, 6H), 2.09 (m, 1H), 1.89 (m, 2H), 1.67 (m, 1H), 1.63 (s, 3H), 1.59 (d, ^2J=14.3 Hz, 1H), 1.54 (ddd, ^2J=14.2 Hz, ^3J=10.9 Hz, 7.1 Hz, 1H), 1.30 (m, 2H), 1.25 (s, 3H), 1.23 (d, ^3J=6.8 Hz, 3H), 1.18 (d, ^3J=6.1 Hz, 3H), 1.12 (d, ^3J=6.6 Hz, 3H), 1.07 (s, 3H), 0.93 (d, ^3J=7.0 Hz, 3H), 0.84 (t, ^3J=7.5 Hz, 3H), 0.78 (d, ^3J=7.5 Hz, 3H); ^{13}C NMR (600 MHz; $CDCl_3$): δ 177.7, 170.7, 154.4, 142.6, 138.1, 137.8, 137.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.6, 128.2, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 128.0, 127.9, 123.3, 100.1, 87.4, 86.2, 81.4, 78.8, 78.2, 78.1, 77.8, 76.2, 75.7, 75.2, 75.1, 74.4, 73.7, 73.4, 71.1, 68.9, 68.5, 63.4, 62.7, 60.9, 55.3, 44.1, 41.6, 40.8, 40.8, 37.0, 36.0, 30.7, 26.5, 26.3, 23.1, 21.5, 21.1, 21.0, 16.3, 16.3, 11.1, 7.6, 7.4; FT-IR (KBr pellet): a broad band at 3418 cm^{-1} $\nu(O_{11}\text{-}H)+\nu(O_{12}\text{-}H)+\nu(O_{2'}\text{-}H)+\nu(O_{4''}\text{-}H)$, 2637 cm^{-1} $\nu(O_6\text{-}H)$, 1752 cm^{-1} $\nu(C_{9'}{=}O)$, 1713 cm^{-1} $\nu(C_1{=}O)_{lactone}$, 1676 cm^{-1} $\nu(C{=}O)_{amide}$, 1548cm^{-1} $\delta(C\text{-}N)_{amide}$, 1454 cm^{-1} $\nu(C{=}C)$, 1260 cm^{-1} $\nu(C\text{-}O\text{-}C)$, 1169 cm^{-1} $\nu(C\text{-}O)$, 1098 cm^{-1} $\nu(C\text{-}O)$, 1046 cm^{-1} $\nu(C\text{-}O)$; HR-MALDI-TOF $[M+H]^+$ = 1188.6571; Elemental analysis $C_{63}H_{92}N_6O_{16}$: calculated: C=63.62%; H=7.80%; N=7.07%; measured C=63.61%; H=7.82%; N=7.06%; HPLC: R_t = 7.39 min (H_2O:CH_3CN:buffer 10:40:50);

5x$_{18}$ Yield*: 21%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.81 (s, 1H), 7.39 (s, 1H), 6.17 (t, ^3J=6.5 Hz, 1H), 5.45 (m, 1H), 5.30 (d, ^2J=12.8 Hz, 1H), 5.19 (d, ^2J=12.8 Hz, 1H), 4.77 (d, ^3J=7.5 Hz, 1H), 4.70 (d, ^3J=10.7 Hz, 1H), 4.60 (dd, ^3J=10.4 Hz, 7.6 Hz, 1H), 4.41 (m, 1H), 3.99 (dd, ^2J=12.4 Hz, ^3J=2.3 Hz, 1H), 3.74 (dd, ^2J=12.5 Hz, ^3J=2.4 Hz, 1H), 3.67 (m, 1H), 3.63 (m, 1H), 3.64 (m, 1H), 3.52 (m, 1H), 3.00 (m, 1H), 2.97 (m, 1H), 2.74 (m, 1H), 2.72 (m, 1H), 2.62 (m, 1H), 2.50 (m, 1H), 2.36 (s, 3H), 2.25 (s, 6H), 2.24 (m, 1H), 2.06 (t, ^2J=11.8 Hz, 1H), 1.93 (d, ^3J=1.1 Hz, 1H), 1.90 (m, 1H), 1.88 (m, 1H), 1.74 (m, 1H), 1.59 (d, ^2J=13.8 Hz, 1H), 1.54 (m, 1H), 1.35 (m, 1H), 1.30 (m, 1H), 1.26 (d, ^3J=6.8 Hz, 3H), 1.25 (s, 3H), 1.23 (d, ^3J=6.0 Hz, 3H), 1.11 (d, ^3J=6.7 Hz, 3H), 1.05 (s, 3H), 0.91 (d, ^3J=6.9 Hz, 3H), 0.85 (t, ^3J=7.4 Hz, 3H), 0.84 (d, ^3J=6.8 Hz, 3H); ^{13}C NMR (400 MHz; $CDCl_3$): δ 177.5, 163.8, 154.5, 150.6, 143.1, 137.9, 124.0, 111.5, 100.4, 89.4, 87.8, 85.4, 78.8, 77.8, 76.2, 75.8, 74.4, 73.4, 71.2, 70.8, 69.0, 63.4, 62.8, 61.7, 61.0, 44.2, 41.8, 40.7, 40.7, 37.6, 36.9, 36.0, 30.1, 26.5, 26.3, 21.5, 21.2, 21.0, 16.3, 16.2, 12.6, 11.1, 7.6, 7.4; HR-MALDI-TOF $[M+H]^+$ = 939.5165; Elemental analysis $C_{44}H_{73}N_7O_{15}$: calculated: C=56.22%; H=7.83%; N=10.43%; measured: C=56.24%; H=7.81%; N=10.42%; HPLC: R_t = 5.78 min (H_2O:CH_3CN:buffer 10:40:50);

Yield* - after purification by column chromatography

B88-LYP (GGA) DFT and MO-G PM6 calculations of antibiotics and their docking models at bacterial ribosomal tunnel

The part of ribosome taken into regard during semi-empirical calculations of macrolides was that of a cube 50x50x50 Å around the binding site i.e. near A2045 (*D. radiodurans*)/ A2103 (*H. marismortui*), indicated earlier on the basis of X-ray studies. [34,35] Before docking of antibiotics, the X-ray models of bacterial ribosomes (*H. marismortui* and *D. radiodurans*) reported by Schlünzen et al. and Tu et al. respectively, have been enriched by the addition of all hydrogen atoms and metal cations as Na^+ and Mg^{2+}, as well as all atoms in these systems have been parameterized /hybridization; charge/. At the next step, the earlier determined conformers of azithromycin and clarithromycin analogs by 2D NMR (^{1}H -^{1}H NOESY, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC and ^{1}H-^{13}C HSQC) and B88-LYP (GGA) DFT (*Scigress* package version *FJ.* 2.4. EU 3.1.9 [36]) studies, shown e.g. in **Figure 5**, have been docked at ribosomal

tunnel on the previously determined coordinates of the aglycone parts of **CLA** and **AZM** from X-ray structures at ribosomes[34,35]. All atoms of the calculated systems distanced from the binding site ~25 Å were locked. Macrolide-ribosome complex structures were optimised by mutual fitting of the macrolide antibiotic and nucleotides of the binding site (near PTC loop) at ribosomal tunnel - first by MM3 (~ 18 000 - 34 000 steps) and finally by MO-G PM6 semi-empirical method (~9 000 – 21 000 steps, with energy gradient not exceeding 5 kcal/mol). In MO-G PM6 calculations the algorithm for a huge molecules was applied. In a result of optimisation of the antibiotic containing the introduced substituent at desosamine in ribosomal tunnel by MO-G PM6 calculations, the two energetic comparable binding sites: S1* (near G2484 of *D. radiodurans*/G2540 of *H. marismortui*) and S2* - the stack of adenylates: A2041-A2042-A2482 (*D. radiodurans*)/ A2099-A2100-A2538 (*H. marismortui*), have been found (**Figures 6** and **7**). Results of the semi-empirical MO-G PM6 calculations were ($\Delta H_f°$, binding energies equal energetic profit between bonded and non-bonded the macrolide to ribosomal tunnel) and respective docking models, shown in **Figures 6** and **7**.

Antibacterial assays

The antimicrobial activity of azithromycin and clarithromycin derivatives was studied against the reference and clinical Gram-positive cocci: *Streptococcus pneumoniae* ATCC 49619, *S. pneumoniae* ATCC 700677, *S. pneumoniae* clinical, *S. pneumoniae* clinical-mucous, *Streptococcus pyogenes* ATCC 19615, *S. pyogenes* clinincal, *Streptococcus mitis/oralis* clinical, *Eneterococcus faecalis* ATCC 29212, *Staphylococcus aureus* MRSA (methicyllin-resistant *Staphylococcus aureus)*, *S. aureus* MLSB (resistance to macrolides, lincosamides, and streptogramin group B), *S. aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228 and *S. epidermidis* ATCC 49134. The used microorganisms were obtained from the ATCC (*American Type Culture Collection)* or were acquired (MRSA, MLS_B, and clinical strains) from the collection of the Chair and Department of Genetics and Pharmaceutical Microbiology at the Poznań University of Medical Sciences, Poland. Minimal Inhibitory Concentration (MIC, mg/L) values were determined independently for **1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e-3u**, **4a-4e**, **4i**, **$5x_1$-$5x_{18}$**, **ERY**, **CLA,** and **AZM** compounds according to the recommendations of the European Society of Clinical Microbiology and Infectious Diseases (EUCAST) using a serial microdilution method on polystyrene plates with Mueller Hinton broth (MHB, Beckton Dickinson) with 5% lysed horse blood (Thermo Scientific) as a medium depending on the strain. Concentrated solutions of the tested compounds were dissolved in DMSO (POCH, Gliwice) and diluted in sterile MHB or MHB with 5% lysed horse blood to obtain the required concentration. The concentrations of the tested compounds in liquid medium ranged from 64 to 0.03125 μg mL^{-1}. The final *inoculum* of all studied organisms added to the serial dilution of assessed compounds was approximately $5.0 \cdot 10^5$ CFU mL^{-1} (Colony Forming Units per mL). Minimal inhibitory concentration (MIC - data shown in **Tables 1**, **13S** and **14S**) was determined after 18±2 h of incubation at 35 ± 1 °C, according to the EUCAST recommendations.

Cytotoxicity assays

Human Dermal Fibroblasts were cultured in DMEM medium. This medium was supplemented with 10% fetal bovine serum, 1% L-glutamine and 1% penicillin/streptomycin solution. The cell line was kept in the incubator at 37 °C in a humidified atmosphere (90% RH) containing 5% CO_2. The optimal plating density of cell line was determined to be 5×10^4. The cell line was obtained from The European Collection of Cell Cultures (ECACC) supplied by Sigma-Aldrich. The protein-staining SRB (Sigma-Aldrich) microculture colorimetric assay, developed by the National Cancer Institute (USA) for in vitro antitumor screening was used in this study to estimate the cell number by providing a sensitive index of total cellular protein content, being linear to cell density. The monolayer cell culture was trypsinized, and the cell count was adjusted to 5×10^4 cells. To each well of the 96-well microtiter plate, 0.1 mL of diluted cell suspension (approximately 10000 cells) was added. After 24h, when a partial monolayer was formed, the supernatant was washed out and 100 μL of six different compound concentrations (0.1, 0.2, 1, 2, 10 and 20 μM) were added to the cells in microtiter plates. The tested compounds were dissolved in DMSO (containing 10% of water) (100 μL), and the content of DMSO did not exceed 0.1%; this concentration was found to be nontoxic to the cell line. The cells were exposed to compounds for 72 h at 37 °C in a humidified atmosphere (90% RH) containing 5% CO_2. After that, 25 μL of 50% trichloroacetic acid was added to the wells and the plated were incubated for 1 h at 4 °C. the plates were then washed out with distilled water to remove traces of medium and next dried by the air. The air-dried plates were stained with 100 μL of 0.4% sulforhodamine B (prepared in 1% acetic acid) and kept for 30 min at room temperature. The unbound dye was removed by rapidly washing with 1% acetic acid and then air-dried overnight. The protein-bound dye was dissolved in 100 μL of 10 mM unbuffered Tris base (pH 10.5) for optical density determination at 490 nm. All cytotoxicity experiments were performed three times. Cell survival was measured as the percentage absorbance compared to the control (nontreated cells). Results of cytotoxicity studies of novel *N*-alkylammonium **AZM** and **CLA** salts are shown in **Table 2**.

Determination of clogP, water solubility and K_d

Derivatives **2e**, **3b**, **3c**, **3e**, **3i**, **3l**, **3r**, **3s**, **4b**, **4c**, **4e**, **4i** were dissolved in HPLC gradient grade water (pH=7, T=25°C) and the calibration curves were determined by measuring absorbance as a function of their concentration with Jenway 7205 UV/visible spectrophotometer. Analytical wavelength for the determination of calibration curves Af(c) and the concentrations c_{H2O} and $c_{octanol}$ on the basis of UV-vis measurements was λ_{max}=210 nm. To determine $clogP_{exp}$ the known amounts of **2e**, **3b**, **3c**, **3e**, **3i**, **3l**, **3r**, **3s**, **4b**, **4c**, **4e**, **4i** were dissolved in 10 mL of octanol to which 10 mL of H_2O was added. The mixture was shaken, vigorously stirred for 1 hour and then separated. In order to determine the concentration of the compound in the aqueous layer, the respective measurement of absorbance was performed. Experimental $clogP_{exp}$ values were calculated according to the following equation: $logP_{exp} = log(c_{octanol}/c_{H2O})$ and shown in **Table 1**. To determine the solubility in the gradient grade water, a known amount of each of **2e**, **3b**, **3c**, **3e**, **3i**, **3l**, **3r**, **3s, 4a-4e**, **4i** derivatives was weighted and respective volumes of H_2O were added (by 0.02 mL) upon vigorous stirring of the solution. The solubility test was performed at least three times for the derivative studied and its result is given in **Table 1**. K_D values were determine by ITC method. Interactions of selected compounds with ribosome was assessed by Isothermal Titration Calorimetry (ITC) method described by Gonzáles et al.[38] Titrations was conducted in an Auto-ITC 200 microcalorimeter. Ribosome and compounds solutions were degassed and loaded into the calorimetric cells to avoid formation of the bubble during stirring. Experiments were carried out with freshly prepared buffer-exchanged protein solutions containing 50 mM Tris-HCl [pH 8], 150 mM NaCl, 10% glycerol and 1% DMSO at 25 °C. Solution of ribosome (20 μM) in the calorimetric cell was titrated with a solution of the corresponding compound (200 μM) located in the injecting syringe. A sequence of 19 injections of 2 μL volume was programmed with a time spacing of 150 s, a stirring speed of 750 rpm, and a reference power of 10 μcal/s in the sample cell.[39,40] The K_A (the association constant in M^{-1} was determined by ITC. Dissociation constant (K_D) was calculated from the equation $K_D = 1/K_A$. The calculated dissociation constants K_D for binding **4e** and **4b** with *E. coli* ribosomes were determined at pH = 7.2.

Copy of ^1H, ^{13}C NMR and FT-IR spectra with full assignment of NMR resonances of all *N*-alkylammonium **AZM** (**1e**, **1o**, **2e**, **2l**, **2o**, **3b**, **3c**, **3e-3u**) and **CLA** (**4a-4e**, **4i**) analogs as well as carbonate-triazole **AZM** derivatives (**$5x_1$-$5x_{18}$**) (**Tables 1S-12S**), copy of 2D NMR spectra needed for evaluation of conformation of new macrolide derivatives, microbiological data of macrolide analogs **$5x_1$-$5x_{18}$** (**Table 14S**). This material is available as **Supporting Information** free of charge *via* the Internet at http://

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Keywords: antibiotics • *click* chemistry • antibacterial • cytotoxicity • drug-ribosome interactions

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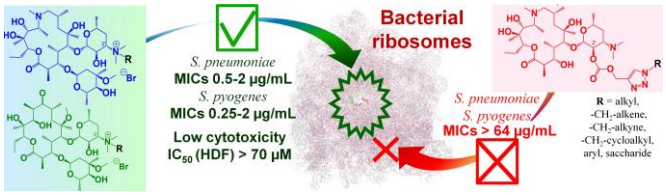
Entry for the Table of Contents



New azithromycin (**AZM**) and clarithromycin (**CLA**) analogs are obtained *via N*-alkylation (S_N2) or nucleophilic substitution at carbonyl/CuAAC. Biological and docking studies together with solubility, *c*logP and K_D, show favorable binding of quaternary **CLA** salts in the ribosomal tunnel and good antibacterial potency against clinical and standard *S. pneumoniae* and *S. pyogenes* (MICs 0.25-0.5 µg/mL), at 3-fold lower toxicity than reference antibiotics.