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Novel ureas and thioureas of 15-membered azalides with antibacterial activity against key respiratory pathogens

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ABSTRACT

The new ureas and thioureas of 15-membered azalides, *N*′′-substituted 9a-(*N*′-carbamoyl-γ-aminopropyl) (**4**), 9a-(*N*′-thiocarbamoyl-γ-aminopropyl) (**6**), 9a-[*N*′-(β-cyanoethyl)-*N*′-(carbamoyl-γ-aminopropyl)] (**8**) and 9a-[*N*′-(β-cyanoethyl)-*N*′-(thiocarbamoyl-γ-aminopropyl)] (**10**) of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A (**2**), were synthesized and structurally characterized by NMR and IR spectroscopic methods and mass spectrometry. The new compounds were evaluated *in vitro* against a panel of erythromycin susceptible and erythromycin-resistant Gram-positive and Gram-negative bacterial strains. These compounds displayed an excellent overall antibacterial *in vitro* activity against erythromycin sensitive Gram-positive strains, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and good against negative strains, *Moraxella catarrhalis* and *Haemophilus influenzae*. In addition, several ureas with naphthyl substituents (**4f**, **4g**, **4h**) showed better activity in comparison to azithromycin against inducible resistant *S. pyogenes*. Ureas with naphthyl substituents **4g**, **4h** and thiourea **8h** displayed moderate activity against constitutively resistant *S. pneumoniae*.

1. Introduction

Macrolides have a long history as effective therapeutic agents for treating infectious diseases [1,2]. They are still in the centre of interest of many research groups and pharmaceutical companies and much effort is directed toward the discovery of new macrolide antibiotics by chemical modification of the existing classes of natural derivatives. The goal is to obtain novel therapeutic agents having an improved overall biological profile with a special emphasis on resistant bacterial strains. Of particular interest are azalides, semisynthetic derivatives of erythromycin A [1,3], which were found to display a wide antimicrobial spectrum and the ability to concentrate within host cells with high accumulation ratios. The predominant mechanisms of resistance to macrolides in Gram-positive microorganisms are target site modifications by methylation that prevents the binding of the antibiotic to the ribosome (encoded by the erm gene), and efflux mechanisms, mediated by the mef (streptococci) and msr (staphylococci) genes. The methylation of the ribosomal RNA bases leads to cross-resistance to macrolides (M), lincosamides (L), and streptogramine B (S_B), the so-called MLS_B phenotype [4]. The continuing emergence of multi-drug-resistant Gram-positive and Gram-negative pathogens imposes a serious threat to the health-care community and intensifies the search for new and more effective agents in order to overcome this problem. Recently, crystal structures of some ribosome–macrolide complexes [5,6] and NMR studies [7] have thrown new light on understanding the principles of how these antibiotics interact with their targets and thus can be useful in the process of designing compounds with bioactivity. Recently published novel 14- to 16-membered 11-azalides and 16-membered 11,12-diazalide, starting from 16-membered macrolides, exhibited strong antibacterial activity against inducible resistant bacteria *Streptococcus pneumoniae* [8,9].

In our previous papers we have reported the synthesis and antibacterial activity of novel sulfonylureas of 15-membered azalides [10] and conjugates of azithromycin and sulfonamides [11] which showed significant improvements in activity against inducible resistant *Streptococcus pyogenes* in comparison with macrolide antibiotic azithromycin. These results encouraged us to continue and extend our investigation on a series of related compounds. The main goal of this research was to expand the range of antimicrobial activity, especially against MLS_B and efflux resistant *S. pyogenes* and

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S. pneumoniae strains by replacing sulfonylcarbamoyl group at the propyl chain with carbamoyl and thiocarbamoyl groups. We believe that this could be a step forward in the discovery of novel bioactive macrolide compound. Hence, the present paper describes the synthesis, structure elucidation, acid stability and antibacterial *in vitro* evaluation of new ureas and thioureas of 15-membered azalides derived from **2**, *e.g.* *N*″-substituted *N*′-(carbamoyl-γ-aminop ropyl) (**4**), *N*′-(thiocarbamoyl-γ-aminopropyl) (**6**), *N*′-(β-cyan oethyl)-*N*′-(carbamoyl-γ-aminopropyl) (**8**) and *N*′-(β-cyanoethyl)-*N*′-(thiocarbamoyl-γ-aminopropyl) (**10**) moieties (Scheme 1).

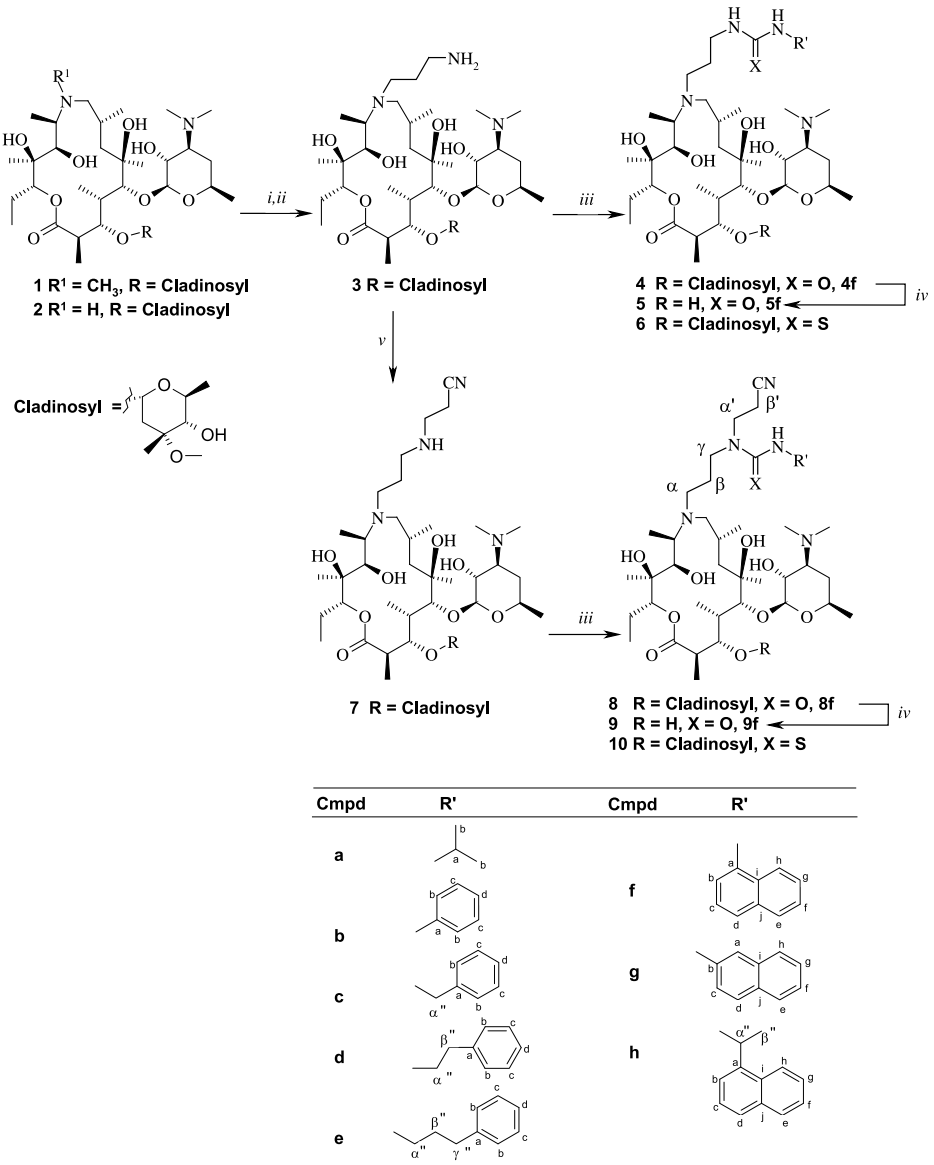
2. Results and discussion

2.1. Chemistry

The addition of isocyanates or thiocyanates to primary and secondary amines is an efficient method for the preparation of substituted ureas and thioureas, respectively.[12] The key intermediates, 9a-(γ-aminopropyl) derivative **3** and 9a-[*N*′-(β-cyan oethyl)-γ-aminopropyl] derivative **7** were prepared by Michael addition of acrylonitrile and catalytic hydrogenation with PtO_2 according to procedure described in the previous paper [10]. *N*″-Aryl substituted 9a-(*N*′-carbamoyl-γ-aminopropyl) (**4**), 9a-(*N*′-thiocarbamoyl-γ-aminopropyl) (**6**), 9a-[*N*′-(β-cyanoethyl)-*N*′-(carbamoyl-γ-aminopropyl)] (**8**) and 9a-[*N*′-(β-cyanoethyl)-*N*′-(thioc arbamoyl-γ-aminopropyl)] (**10**) derivatives were obtained by the reaction of corresponding isocyanates and thioisocyanates with amines **3** and **7** in high yield. Reaction proceeded smoothly in an aprotic solvent and at room temperature to form less polar products (Scheme 1).

2.2. Structural characterization

The structures of all synthesized compounds were determined by IR and NMR spectroscopies and mass spectrometry. In the IR spectra of the novel ureas **4** and **6** and thioureas **8** and **10** new



Scheme 1. Synthesis of novel ureas and thioureas of 15-membered azalides. Reagents and conditions: *i*, acrylonitrile, 60 °C, 10 h; *ii*, H_2/5% Pt/C, 5% hydrochloric acid, 4 bar, r.t., 40 h; *iii*, alkyl or aryl isocyanate/isothiocyanate, CH_2Cl_2, room temperature, 1 h; *iv*, 1 M hydrochloric acid, r.t.; *v*, 1 eq acrylonitrile, methanol, reflux, 10 h.

bands were observed at approximately 1681–1645 cm^{-1} and 1549–1557 cm^{-1} which corresponded to ureido group C═O stretching vibrations. The bands at approximately 1537–1552 cm^{-1} were diagnostic for the presence of a thioureido group C═S. In the IR spectrum absorption bands of compounds **8** and **10** observed at approximately 2249 cm^{-1} were assigned to C≡N stretching vibrations.

The assignments of proton and carbon chemical shifts were made by a combined use of one- (^{1}H and APT) and two-dimensional (gCOSY, gHSQC and gHMBC) NMR spectra. Carbon and proton chemical shifts of all compounds are given in the Experimental part. The appearance of new signals with respect to **2** was observed in ^{13}C NMR spectrum indicating the presence of carbamoyl (δ_C 154.1–159.4 ppm) and thiocarbamoyl (δ_C 180.8–183.3 ppm) groups. With respect to **2**, additional signals at ~48 ppm (CH_2-α), ~27 ppm (CH_2-β) and ~47 ppm (CH_2-γ) as well as those at ~44 ppm (CH_2-α′), ~17 ppm (CH_2-β′) and ~120 ppm (C≡N) confirmed the presence of the γ-aminopropyl chain and β-cyan oethyl chain, respectively. The substitutions at 9a-N and C-γ-NH_2 were confirmed by changes in the chemical shifts of carbons at positions 9 and 10 of the azalide aglycon ring and C-γ of the propyl chain in comparison with the parent compounds **2**, **3** and **7**. Changes in chemical shifts of CH_2-γ carbons in ureas **4** and **6** and thioureas **8** and **10** indicated structural differences imposed by the inserted ureido and thioureido groups (at 38–39 ppm and 43–44 ppm, respectively). The presence of alkyl and aryl substituents was confirmed by characteristic singlets observed in the regions 118–142 ppm in the carbon spectrum and 7.0–8.3 ppm in the proton spectrum. In the HMBC spectra of the ureas/thiourea the observed cross-peaks between carbamoyl/thiocarbamoyl groups and three pairs of methylene protons in the propyl and cyanoethyl chains (CH_2-γ, CH_2-α″ and CH_2-α′) were indicators of the sites where substitution occurred.

Mass measurement accuracy, as experimentally determined, was within the specified limit for the instrument used (better than 5 ppm), in experiments performed with intact compounds, while the results obtained by MS/MS experiments were in the range of 5 ± 3.5 ppm. Deduced elemental compositions of fragment ions with theoretically calculated masses (Fig. 1) indicated that **10d** protonated precursor ion fragmentation with *m*/*z* 1008.6318 most likely began with a single- or a two-step fragmentation of the complete side chain. In the first step, a cleavage of a thiocarbamoyl group initiated dissociation (*m*/*z* 1008.6318 → 845.5901) followed by a complete side chain elimination (*m*/*z* 845.5901 → 735.5062). Additional support for the predicted fragmentation that occurred through a single-step fragmentation pathway was the side chain product ion detected at *m*/*z* 274.1441. The result of both fragmentation pathways with the same outcome pointed toward the cleavage at position 9a-*N* as the most preferable position for fragmentation, and further product ion formation after glycosidic bond cleavages (*m*/*z* 735.5062 → 420.2937 desosamine and cladinose and *m*/*z* 735.5062 → 577.4101 cladinose cleavage). Neutral losses of water molecules indicated the number of labile hydroxyl groups with maximum losses of three water molecules, *m*/*z* 420.2937 → *m*/*z* 402.2830 → *m*/*z* 384.2742 → *m*/*z* 366.2622. Similar fragmentation pattern was observed for other compounds too.

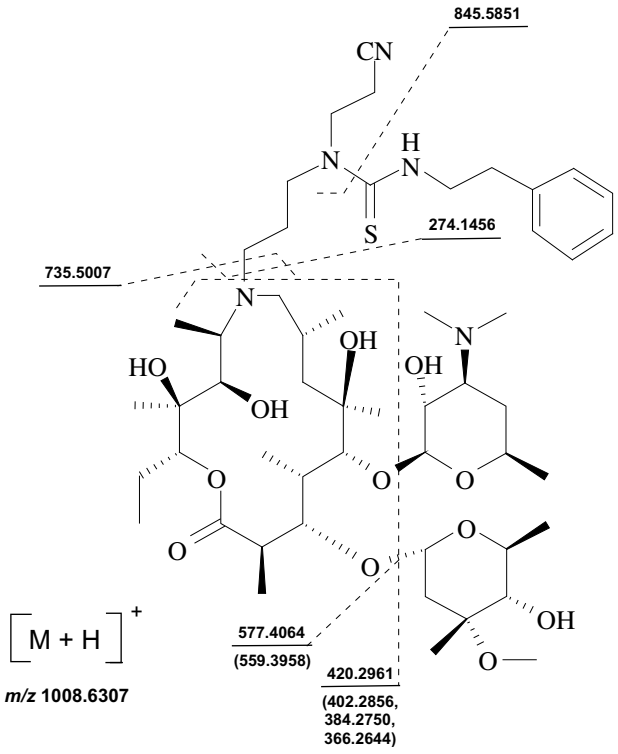


Fig. 1. Proposed fragmentation pattern of the thiourea **10d** based on the accurate mass MS/MS experiments with theoretically calculated masses. Values in parentheses represent the obtained loss of water after dissociation.

2.3. Acid stability

It was reported that in aqueous acidic media erythromycin derivatives underwent intramolecular cyclization reactions [13,14] to form inactive products. The decomposition of azithromycin [15] and its sulfonamido conjugates [11] included only hydrolysis of the cladinose sugar glycosidic bond leading to the inactive decladinosyl derivatives which was found to be a common characteristic of macrolide [16,17] and azalide compounds [18].

The acidic stability studies of the active *N*′-[(1-naphthyl)carbamoyl-γ-aminopropyl] **4f** and *N*′-[(β-cyanoethyl)-*N*′-(1-naphthyl)carbamoyl-γ-aminopropyl] **8f** derivatives were carried out in 0.01 M HCl aqueous hydrochloric acid at 37 °C as a model of artificial gastric juice. We used here LC/UV and LC/MS methods to study kinetics of hydrolysis for ureas **4f** and **8f** and their degradation products. The mass spectra of the reaction mixtures after 10 h showed only precursor ions at *m*/*z* 803.1 and 856.1, which were indicative for the cleavage of the cladinose sugars giving decladinosyl compounds **5f** and **9f**, respectively. No further degradation products were observed under the studied conditions as previously observed for azithromycin and its sulfonamido conjugates [11,15]. The regioselective hydrolysis of **4f** and **8f** in 1.0 M hydrochloric acid at room temperature, furnished the decladinosyl derivatives **5f** and **9f**, alternatively prepared as the analytical standards.

The hydrolytic degradation of **5f** and **9f** followed pseudo first-order kinetics as observed for the related compounds [9]. Reaction rate constants (*k*) were determined from the exponential fit analysis of the plot of the reactant concentration (**4f** and **8f**) versus time. The calculated rate constants for 50% decay ($t_{1/2}$) are listed in Table 1.

The activation energies of hydrolysis of glycosidic bonds for **5f** and **9f** were also determined and amounted to 91.1 kJ/mol and

Table 1
Pseudo first-order reaction rate constants and $t_{1/2}$ values for **4f** and **8f**.

t/°C	**4f**		**8f**	
	k/min^{-1}	$t_{1/2}$[a]/min	k/min^{-1}	$t_{1/2}$[a]/min
37	5.83×10^{-3}	119	6.41×10^{-3}	108

[a] Calculated according to $t_{1/2} = \ln 2/k$.

88.5 kJ/mol, respectively (Fig. 2). These values were similar to those obtained for azithromycin 105.9 kJ/mol [13] and its sulphonamide conjugates (90.5 kJ/mol and 89.9 kJ/mol) [11].

2.4. In vitro *antibacterial activity*

The *in vitro* minimum inhibitory concentrations (MICs) for ureas **4** and **8**, thioureas **6**, **10** and azithromycin as a selected standard, against common pathogens are listed in Tables 2 and 3. Ureas **4** and **8** and thioureas **6** and **10** showed a significant improvement in antibacterial activity against all tested macrolide-susceptible and resistant bacteria (Tables 2 and 3) in comparison with carbamoyl/thiocarbamoyl derivatives [12], sulfonylcarbamoyl derivatives [10] and azithromycin–sulfonamide conjugates [11]. Several ureas with naphthyl substituents (**4f**, **4g**, **4h**) were superior *in vitro* to the azithromycin against inducible resistant *S. pyogenes* with MICs 2 μg/ml (Tables 2 and 3). In Tables 2 and 3 it is clearly seen that ureas **4f**, **4g** and thioureas **6c**, **6d**, **6e** and **6f** possess good activity against efflux resistant *S. pyogenes*, comparable to azithromycin. In general, all tested compounds had high *in vitro* activity against erythromycin susceptible Gram-positive aerobes, *S. pneumoniae* and *S. pyogenes* (MIC $\leq$ 0.125 μg/ml). Ureas **4** and **8** and thioureas **6** and **10** exhibited excellent activity against susceptible *Staphylococcus aureus*, but lacked activity against resistant *S. aureus* strains. Ureas **4f**, **4g** and thiourea **6f** also showed *in vitro* activity against efflux resistant *S. pneumoniae* with MICs 4 μg/ml and their activities were comparable with those observed for azithromycin. Ureas **4g**, **4h** and **8h** showed moderate activity against cMLS *S. pneumoniae*.

In vitro activities of ureas **4** and **8**, thioureas **6** and **10** against key community-acquired Gram-negative respiratory pathogens were improved in comparison with sulfonylureas [10] and azithromycin–sulfonamide conjugates [11]. Ureas **4f**, **4g** and **4h** demonstrated high activity against *Moraxella catarrhalis*. Naphthyl substituted ureas **4f**, **4g** and **4h** showed better activity against Gram-negative pathogens involved in respiratory tract infections (RTIs), *M. catarrhalis* and *Haemophilus influenzae* than derivatives with phenyl ring on the alkyl side chain **4b**–**4d**. In the case of phenyl–ethyl substituents in **4d** and **6d** the presence of thiocarbamoyl moiety seemed to improve activity against *H. influenzae*, MIC 16 μg/ml and 2 μg/ml, respectively. The urea **8** with cyanoethyl chain showed similar antibacterial activity in comparison to the urea **4**.

Surprisingly, the observed increase of antibacterial activity in the series of ureas and thioureas **4**, **6**, **8** and **10** in comparison with those of their analogs **11** and **12** [12] was opposite to the results obtained for the sulfonylcarbamoyl derivatives **13**, **14** and **15** [10,11] where a decrease of activity was found when sulfonylcarbamoyl moiety was further away from the azalide ring (Fig. 3).

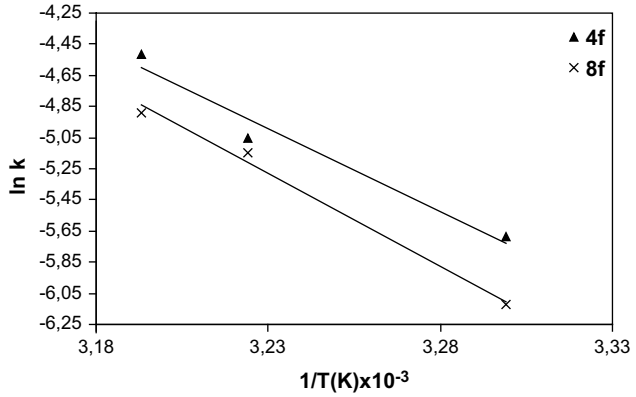


Fig. 2. Arrhenius plot of temperature versus pseudo first-order reaction rates of **4fa** and **8f**.

Decladinosyl derivatives **5f** and **9f**, obtained by the hydrolysis in acidic media, were tested only against panel of *S. pneumoniae* strains. As we expected decladinosyl urea derivative **9f** did not show activity against tested strains. However, decladinosyl urea derivative **5f** showed significant activity against erythromycin susceptible *S. pneumoniae* strain (1 μg/ml), as well as efflux resistant *S. pneumoniae* strain (8 μg/ml) comparable to azithromycin.

In conclusion, the introduction of carbamoyl and thiocarbamoyl group to the 9a position of azithromycin like azalide skeleton via propyl linker proved to be promising method to tackle the resistance problems. As a result of a preliminary optimization of an alkyl/aryl moiety at the carbamoyl and thiocarbamoyl group, several new ureas with naphthyl substituents (**4f**, **4g**, **4h**) have been prepared, which showed better activity against inducible resistant *S. pyogenes* in comparison to azithromycin. In acidic conditions compounds exhibited azithromycin like stability. Novel ureas and thioureas of 15-membered azalides showed their potential to serve as a good platform for further investigation in order to discover new derivatives having an improved overall biological profile with a special emphasis on resistant bacterial strains.

3. Experimental

3.1. General methods

TLC was performed on Merck 60 F254 plates using CH_2Cl_2:CH_3OH:NH_3 (25%) = 90:9:1.5 as eluents. Column chromatography was performed on Merck silica gel 60 (0.043–0.060 mm). The purity of the isolated compounds was better than 90% according to LC/MS measurements. ESI-MS/MS spectra were obtained on Q-TOF Micromass spectrometer equipped with the lock-spray (Waters Corporation, Manchester, UK) connected to an CapLC liquid chromatography system (Waters Corporation) under the following conditions: positive ion mode, source temp 450 °C, capillary 3.4 kV, sample cone 30 V and collision energy 40 eV. Leucine enkephalin ($C_{28}H_{37}N_2O_7$) at concentration 100 pg/μl dissolved in the solution of acetonitrile and water (1:1, v/v) with addition of 0.1% formic acid (v/v) was infused into the reference sprayer as internal lock-mass standard (*m*/*z* 556.2771). Mass concentration of 1 μl solution of analyte injected onto the column was 0.1 μg/ml (Waters Symmetry C_{18}, 5 μm 0.32 × 150 mm). The analyte was isocratically eluted over 10 min with mixture of acetonitrile and water (8:2, v/v) with addition of 0.1% formic acid (v/v). Flow rate was 10 μl min^{-1} and the analyte was diluted in the mobile phase.

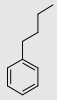
3.2. Spectroscopic measurements

NMR experiments were carried out on a Bruker Avance DRX500 spectrometer operating at 500.13 MHz for ^1H, and 125.77 MHz, for ^{13}C, respectively, with a 5 mm diameter inverse detection probe and a *z*-axis gradient coil. Standard spectral conditions were used. The solvents were pyridine-d_5 and $CDCl_3$ and all experiments were performed at ambient temperature. TMS was used as the internal standard. IR spectra were recorded in KBr pellets on a Nicolet Magna 760 FT-IR spectrometer. The number of scans was 16 and the resolution was 4 cm^{-1}.

3.3. General procedure for the preparation of ureas ***4***, ***8*** and thioureas ***6***, ***10***

To the solution of **3** or **7** (1.84 mmol) in dichloromethane (30 ml) isocyanate or isothiocyanate (1.97 mmol) was added and the reaction mixture was stirred about 1 h at the temperature 0–5 °C.

Table 2
Antibacterial activity (MIC/μg ml^{-1}) of carbamoyl and thiocarbamoyl analogs **4** and **6**.

Compounds	**4a**	**4b**	**4c**	**4d**	**4f**	**4g**	**4h**	**6b**	**6c**	**6d**	**6e**	**6f**	**1**
X	O	O	O	O	O	O	O	S	S	S	S	S	
R′													
S. aureus ATCC 29213	2	0.25	0.5	1	0.5	1	1	0.5	0.5	1	0.5	1	0.5
S. pneumoniae	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125
S. pneumoniae-M	32	16	16	32	4	4	16	16	8	8	8	4	8
S. pneumoniae-cMLS	>64	>64	>64	>64	>64	16	16	>64	64	>64	>64	>64	64
S. pyogenes	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125
S. pyogenes-iMLS	8	4	4	8	2	2	2	8	4	4	4	4	8
S. pyogenes-M	32	16	8	32	4	4	8	16	4	4	4	4	4
M. catarrhalis ATCC 23246	1	2	1	2	0.5	0.25	0.25	2	1	1	1	1	≤0.125
H. influenzae ATCC 49247	16	8	2	16	1	2	2	4	2	2	2	2	1
E. faecalis ATCC 29212	32	16	16	16	4	8	8	8	8	16	16	8	8
E. coli ATCC 25922	16	8	8	16	8	16	32	8	16	32	16	8	2

iMLS: inducible resistance to macrolide, lincosamide and streptogramin (MLS) antibiotics, cMLS: constitutive MLS resistance, M: efflux mediated macrolide resistance.

The crude product was evaporated, wherefrom by column chromatography on silica gel using solvent system CH_2Cl_2:CH_3OH:NH_3 (25%) = 90:9:1.5 pure compound was obtained.

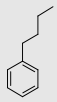
3.3.1. 9-Deoxo-9-dihydro-9a-(N′-isopropylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerythromycin A (**4a**)

Yield 76.2%. MS *m*/*z*: (ES): $MH^+ = 877.2$. IR (KBr) [ν/cm^{-1}]: 3410, 2972, 2937, 1730, 1672, 1598, 1553, 1500, 1458, 1379, 1167, 1054. ^{1}H NMR (pyridine-d_5) δ 3.12 (1H, H-2), 4.76 (1H, H-3), 2.52 (1H, H-4), 4.16 (1H, H-5), 1.95, 1.6 (2H, H-7), 2.23 (1H, H-8), 2.73; 2.24 (2H, H-9), 3.09 (1H, H-10), 4.22 (1H, H-11), 5.44 (1H, H-13), 1.74; 2.15 (2H, H-14), 0.97 (3H, H-15), 5.00 (1H, H-1′), 3.63 (1H, H-2′), 2.71 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.37; 1.17 (2H, H-4′), 4.01 (1H, H-5′), 5.29 (1H, H-1″), 2.45; 1.53 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.65 (1H, H-5″), 1.37 (3H, 2 Me), 1.58 (3H, 4 Me), 1.76 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.39 (3H, 10 Me), 1.40 (3H, 12 Me), 1.16 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.68 (3H, 5″ Me), 3.23; 2.78 (2H, α-CH_2), 1.95 (2H, β-CH_2), 3.43; 3.37 (2H, γ-CH_2), 4.24 (1H, isopropyl, CH, a), 1.15 (3H, isopropyl, CH_3, b); ^{13}C NMR (pyridine-d5) δ 177.7 (C-1), 45.5 (C-2), 79.3 (C-3), 42.0 (C-4), 84.1 (C-5), 74.7 (C-6), 42 (C-7), 28 (C-8), 64 (C-9), 61 (C-10), 75.7 (C-11), 75.4 (C-12), 77.9 (C-13), 22.4 (C-14), 11.6 (C-15), 103.6 (C-1′), 71.8 (C-2′), 65.8 (C-3′), 40.6 (3′ NMe_2), 30.6 (C-4′), 68.3 (C-5′), 96.1 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.9 (C-4″), 66.2 (C-5″), 15.6 (2 Me), 10.4 (5 Me), 29.0 (6 Me), 22.7 (8 Me), 9.8 (10 Me), 18.4 (12 Me), 23.6 (5′ Me), 21.6 (3″ Me), 19.5 (5″ Me), 49 (α-CH_2); 28.2 (β-CH_2), 39.1 (γ-CH_2), 158.8 (NHCONH), 42.0 (CH, a), 23.6 (CH_3, b).

3.3.2. 9-Deoxo-9-dihydro-9a-(N′-phenylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerythromycin A (**4b**)

Yield 51.2%. MS *m*/*z*: (ES): $MH^+ = 911.2$. IR (KBr) [ν/cm^{-1}]: 3410, 2972, 2937, 1730, 1672, 1598, 1553, 1500, 1458, 1379, 1167, 1054, 897.753. ^{1}H NMR (pyridine-d_5) δ 3.13 (1H, H-2), 4.76 (1H, H-3), 2.51 (1H, H-4), 4.16 (1H, H-5), 1.92; 1.60 (2H, H-7), 2.24 (1H, H-8), 2.73; 2.23 (2H, H-9), 3.09 (1H, H-10), 4.20 (1H, H-11), 5.43 (1H, H-13), 2.17, 1.84 (2H, H-14), 0.95 (3H, H-15), 4.98 (1H, H-1′), 3.62 (1H, H-2′), 2.70 (1H, H-3′), 2.17 (6H, 3′ NMe_2), 1.41; 1.15 (2H, H-4′), 3.99 (1H, H-5′), 5.26 (1H, H-1″), 2.43; 1.52 (2H, H-2″), 3.50 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.64 (1H, H-5″), 1.36 (3H, 2 Me), 1.59 (3H, 4 Me), 1.75 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.37 (3H, 10 Me), 1.40 (3H, 12 Me), 1.35 (3H, 5′ Me), 1.32 (3H, 3″ Me), 1.69 (3H, 5″ Me), 3.26; 2.75 (2H, α-CH_2), 1.96; (2H, β-CH_2), 3.45; 3.39 (2H, γ-CH_2), 7.88 (2H, phenyl, b), 7.30 (2H, phenyl, c), 6.98 (1H, phenyl, d), 6.52 (NH), 9.16 (NH); ^{13}C NMR (pyridine-d5) δ 177.7 (C-1), 45.5 (C-2), 79.5 (C-3), 41.9 (C-4),

Table 3
Antibacterial activity (MIC/μg ml^{-1}) of carbamoyl and thiocarbamoyl analogs **8** and **10**.

Compounds	**8a**	**8b**	**8c**	**8d**	**8f**	**8g**	**8h**	**10b**	**10c**	**10d**	**10e**	**10f**	**1**
X	O	O	O	O	O	O	O	S	S	S	S	S	
R′													
S. aureus ATCC 29213	4	1	2	4	1	1	2	2	1	1	1	4	0.5
S. pneumoniae	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125
S. pneumoniae-M	32	32	16	64	16	16	32	32	16	32	32	16	8
S. pneumoniae-cMLS	>64	>64	64	>64	64	32	16	>64	64	64	32	64	64
S. pyogenes	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125
S. pyogenes-iMLS	32	16	16	32	8	16	8	32	16	8	8	32	8
S. pyogenes-M	32	32	8	64	8	8	8	32	8	16	16	32	4
M. catarrhalis ATCC 23246	0.5	4	0.5	16	0.5	1	0.5	4	1	2	4	4	≤0.125
H. influenzae ATCC 49247	4	8	4	32	4	2	2	16	4	4	4	8	1
E. faecalis ATCC 29212	64	32	32	64	16	16	16	>64	32	32	16	32	8
E. coli ATCC 25922	16	32	8	>64	8	32	32	>64	16	16	16	8	2

iMLS: inducible resistance to macrolide, lincosamide and streptogramin (MLS) antibiotics, cMLS: constitutive MLS resistance, M: efflux mediated macrolide resistance.

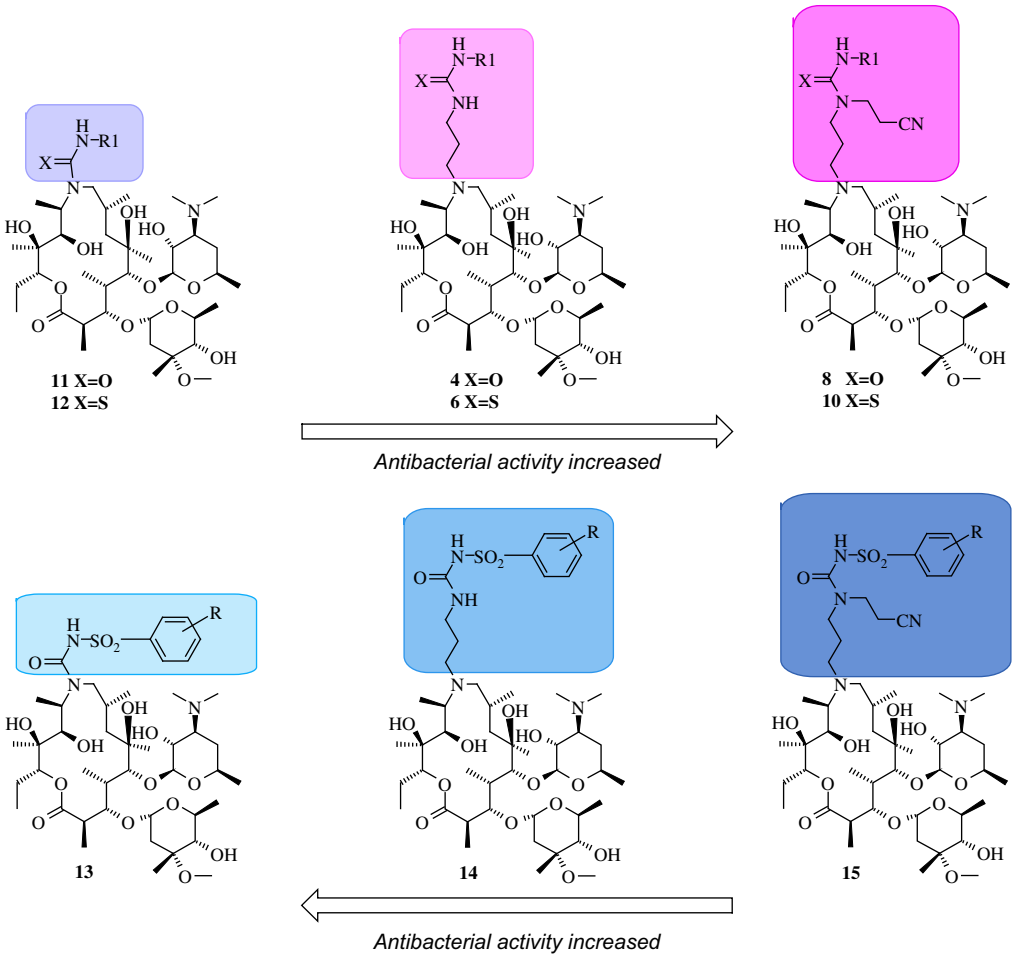


Fig. 3. Antibacterial activities of urea and thiourea derivatives of 15-membered azalides in comparison to sulfonylurea analogs.

84.1 (C-5), 74.7 (C-6), 41.7 (C-7), 29.1 (C-8), 64 (C-9), 64 (C-10), 75.9 (C-11), 73.7 (C-12), 77.9 (C-13), 22.4 (C-14), 11.5 (C-15), 103.6 (C-1′), 71.8 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.4 (C-4′), 68.3 (C-5′), 96.2 (C-1″), 35.7 (C-2″), 75.4 (C-3″), 49.7 (3″ OMe), 78.8 (C-4″), 66.2 (C-5″), 15.7 (2 Me), 10.4 (4 Me), 28.3 (6 Me), 22.6 (8 Me), 9.6 (10 Me), 18.4 (12 Me), 22.0 (5′ Me), 19.5 (3″ Me), 21.6 (5″ Me), 49.8 (α-CH_2); 29.2 (β-CH_2), 39.0 (γ-CH_2), 156.5 (NHCONH), 141.9 (phenyl, a), 129.2 (phenyl, c), 121.7 (phenyl, d), 118.9 (phenyl, b).

3.3.3. 9-Deoxo-9-dihydro-9a-(N′-benzylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerythromycin A (**4c**)

Yield 47.2%. MS *m*/*z*: (ES): $MH^+ = 925.2$. IR (KBr) [ν/cm^{-1}]: 3410, 2972, 2937, 1730, 1672, 1598, 1553, 1500, 1458, 1379, 1167; ^{1}H NMR (pyridine-d_5) δ 3.12 (1H, H-2), 4.77 (1H, H-3), 2.53 (1H, H-4), 4.17 (1H, H-5), 1.95; 2.53 (2H, H-7), 2.2 (1H, H-8), 2.79; 2.26 (2H, H-9), 3.2 (1H, H-10), 4.22 (1H, H-11), 5.44 (1H, H-13), 1.73; 2.15 (2H, H-14), 0.96 (3H, H-15), 5.00 (1H, H-1′), 3.63 (1H, H-2′), 2.73 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.39; 1.16 (2H, H-4′), 4.01 (1H, H-5′), 5.28 (1H, H-1″), 2.43; 1.50 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.68 (1H, H-5″), 1.35 (3H, 2 Me), 1.58 (3H, 4 Me), 1.27 (3H, 6 Me), 0.93 (1H, H-8 Me), 1.37 (3H, 10 Me), 1.41 (3H, 12 Me), 1.26 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.69 (3H, 5″ Me), 3.3, 2.79 (2H, α-CH_2), 2.25; 1.90 (2H, β-CH_2), 3.5; 3.4 (2H, γ-CH_2), 6.96 (1H, NH), 6.53 (1H, NH), 7.54 (2H, phenyl, b), 7.32 (2H, phenyl, c), 7.22 (1H, phenyl, d), 4.64 (2H, α″-CH_2); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 44.7 (C-2), 79.4 (C-3), 42.0 (C-4), 84.1 (C-5), 74.7 (C-6), 41.8 (C-7), 28.3 (C-8), NA (C-9), 61.5 (C-10), 75.7 (C-11), 75.4 (C-12), 77.9 (C-13), 22.4 (C-14), 11.1 (C-15), 103.6 (C-1′), 71.8 (C-2′), 65.8 (C-3′), 40.6 (3′ NMe_2), 30.7 (C-4′), 68.3 (C-5′), 96.2 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.8 (C-4″), 66.6 (C-5″), 15.6 (2 Me), 10.4 (4 Me), 29.0 (6 Me), 22.7 (8 Me), 9.7 (10 Me), 18.4 (12 Me), 22.0 (5′ Me), 21.6 (3″ Me), 19.5 (5″ Me), 49 (α-CH_2); 29.2 (β-CH_2), 39.4 (γ-CH_2), 159.4 (NHCONH), 141.9 (phenyl, a), 128.7 (phenyl, c), 127.8 (phenyl, b), 127.0 (phenyl, d), 44.3 (α″-CH_2).

3.3.4. 9-Deoxo-9-dihydro-9a-(N′-phenylethylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerythromycin A (**4d**)

Yield 53.2%. MS *m*/*z*: (ES): $MH^+ = 939.3$. IR (KBr) [ν/cm^{-1}]: 3444, 2972, 2937, 1729, 1672, 1598, 1553, 1500, 1458, 1379, 1168. ^{1}H NMR (pyridine-d_5) δ 2.86 (1H, H-2), 4.19 (1H, H-3), 2.1 (1H, H-4), 3.64 (1H, H-5), 2.02; 1.74 (2H, H-7), 2.04 (1H, H-8), 2.7; 2.19 (2H, H-9), 2.85 (1H, H-10), 3.74 (1H, H-11), 4.69 (1H, H-13), 1.89, 1.49 (2H, H-14), 0.89 (3H, H-15), 4.43 (1H, H-1′), 3.24 (1H, H-2′), 2.46 (1H, H-3′), 2.30 (6H, 3′ NMe_2), 1.68; 1.25 (2H, H-4′), 3.50 (1H, H-5′), 4.97 (1H, H-1″), 2.35; 1.53 (2H, H-2″), 3.32 (3H, 3″ OMe), 2.99 (1H, H-4″), 4.07 (1H, H-5″), 1.21 (3H, 2 Me), 1.10 (3H, 4 Me), 1.35 (3H, 6 Me), 0.98 (1H, H-8 Me), 1.13 (3H, 10 Me), 1.08 (3H, 12 Me), 1.22 (3H, 5′ Me), 1.24 (3H, 3″ Me), 1.30 (3H, 5″ Me), 3.4; 2.8 (2H, α-CH_2), 1.75 (2H, β-CH_2), 3.22; 3.16 (2H, γ-CH_2), 3.41 (2H, α″-CH_2), 2.82 (2H, β″-CH_2), 7.28 (1H, phenyl, d), 7.22 (2H, phenyl, c), 7.19 (1H, phenyl, b); ^{13}C NMR (pyridine-d_5) δ 178.1 (C-1), 44.9 (C-2), 79.4 (C-3), 40.7 (C-4), 83.3 (C-5), 74.7 (C-6), 40.5 (C-7), 28.7 (C-8), 64.5 (C-9), 62 (C-10), 73.0 (C-11), 74.7 (C-12), 78.0 (C-13), 21.2 (C-14), 11.1 (C-15), 103.1 (C-1′), 70.8 (C-2′), 65.7 (C-3′), 40.4 (3′ NMe_2), 28.0 (C-4′), 68.9 (C-5′),

95.8 (C-1″), 35.0 (C-2″), 72.8 (C-3″), 49.5 (3″ OMe), 77.9 (C-4″), 65.9 (C-5″), 15.2 (2 Me), 9.4 (4 Me), 27.0 (6 Me), 23.0 (8 Me), 7.9 (10 Me), 16.5 (12 Me), 21.4 (5′ Me), 21.5 (3″ Me), 18.4 (5″ Me), 49.1 (α-CH_2); 28.5 (β-CH_2), 38.7 (γ-CH_2), 158.8 (NHCONH), 41.8 (α″-CH_2); 36.7 (β″-CH_2), 139.7 (phenyl, a), 128.9 (phenyl, c), 128.4 (phenyl, d), 126.1 (phenyl, b).

3.3.5. 9-Deoxo-9-dihydro-9a-[N′-(1-naphthyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**4f**)

Yield 55.2%. MS *m*/*z*: (ES): $MH^+ = 961.3$. IR (KBr) [ν/cm^{-1}]: 3390, 2972, 2937, 1727, 1660, 1549, 1456, 1378, 1260, 1167, 1053, 900, 792, 773. ^{1}H NMR (pyridine-d_5) δ 3.12 (1H, H-2), 4.76 (1H, H-3), 2.52 (1H, H-4), 4.16 (1H, H-5), 1.95, 1.59 (2H, H-7), 2.26 (1H, H-8), 2.73; 2.24 (2H, H-9), 3.09 (1H, H-10), 4.22 (1H, H-11), 5.44 (1H, H-13), 1.74; 2.15 (2H, H-14), 0.97 (3H, H-15), 5.00 (1H, H-1′), 3.63 (1H, H-2′), 2.71 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.37; 1.17 (2H, H-4′), 4.01 (1H, H-5′), 5.29 (1H, H-1″), 2.45; 1.53 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.65 (1H, H-5″), 1.37 (3H, 2 Me), 1.58 (3H, 4 Me), 1.76 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.39 (3H, 10 Me), 1.40 (3H, 12 Me), 1.16 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.68 (3H, 5″ Me), 3.23; 2.78 (2H, α-CH_2), 1.87 (2H, β-CH_2), 3.43; 3.37 (2H, γ-CH_2), 7.61 (1H, b, naphthyl), 7.49 (1H, c, naphthyl), 8.45 (1H, d, naphthyl), 8.31 (1H, e, naphthyl), 7.44 (1H, f, naphthyl), 7.89 (1H, g, naphthyl), 7.86 (1H, h, naphthyl); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 45.5 (C-2), 79.4 (C-3), 41.9 (C-4), 84.1 (C-5), 74.7 (C-6), 42 (C-7), 28.2 (C-8), 64.6 (C-9), 61.8 (C-10), 75.8 (C-11), 75.4 (C-12), 77.9 (C-13), 22.4 (C-14), 11.5 (C-15), 103.6 (C-1′), 71.7 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.4 (C-4′), 68.3 (C-5′), 96.1 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.8 (C-4″), 66.2 (C-5″), 15.6 (2 Me), 10.4 (4 Me), 29.0 (6 Me), 22.7 (8 Me), 9.8 (10 Me), 18.4 (12 Me), 23.6 (5′ Me), 21.6 (3″ Me), 19.5 (5″ Me), 49 (α-CH_2); 29.2 (β-CH_2), 39.1 (γ-CH_2), 157.2 (NHCONH), 128.8 (CH, h, naphthyl), 127.9 (C, i, naphthyl), 126.5 (CH, c, naphthyl), 126.1 (CH, g, naphthyl), 125.8 (CH, f, naphthyl), 123.0 (C, j, naphthyl), 122.5 (CH, e, naphthyl), 119.5 (CH, d, naphthyl), 123.5 (CH, b, naphthyl).

3.3.6. 9-Deoxo-9-dihydro-9a-[N′-(2-naphthyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**4g**)

Yield 55.2%. MS *m*/*z*: (ES): $MH^+ = 961.3$. IR (KBr) [ν/cm^{-1}]: 3408, 2969, 2934, 1728, 1681, 1557, 1456, 1379, 1279, 1167, 1053, 1013, 897, 746. ^{1}H NMR (pyridine-d_5) δ 2.90 (1H, H-2), 4.18 (1H, H-3), 2.45 (1H, H-4), 3.65 (1H, H-5), 1.78, 1.42 (2H, H-7), 2.07 (1H, H-8), 2.76; 2.24 (2H, H-9), 3.72 (1H, H-11), 4.72 (1H, H-13), 1.89; 1.49 (2H, H-14), 0.89 (3H, H-15), 4.42 (1H, H-1′), 3.23 (1H, H-2′), 2.53 (1H, H-3′), 2.28 (6H, 3′ NMe_2), 1.61; 1.22 (2H, H-4′), 3.50 (1H, H-5′), 4.95 (1H, H-1″), 2.33; 1.51 (2H, H-2″), 3.31 (3H, 3″ OMe), 3.03 (1H, H-4″), 4.09 (1H, H-5″), 1.21 (3H, 2 Me), 1.09 (3H, 4 Me), 1.37 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.18 (3H, 10 Me), 1.07 (3H, 12 Me), 1.20 (3H, 5′ Me), 1.23 (3H, 3″ Me), 1.34 (3H, 5″ Me), 2.54 (2H, α-CH_2), 1.78 (2H, β-CH_2), 3.33; 3.18 (2H, γ-CH_2), 8.04 (1H, naphthyl, h), 7.72 (1H, naphthyl, d), 7.69 (1H, naphthyl, g), 7.53 (1H, naphthyl, c), 7.50 (1H, naphthyl, b), 7.38 (1H, naphthyl, f), 7.28 (1H, naphthyl, e); ^{13}C NMR (pyridine-d_5) δ 178.0 (C-1), 44.9 (C-2), 79.6 (C-3), 40.4 (C-4), 84 (C-5), 72.7 (C-6), 41 (C-7), 28.7 (C-8), 65 (C-9), 62 (C-10), 75 (C-11), 74.8 (C-12), 77.9 (C-13), 21.2 (C-14), 11.1 (C-15), 103.2 (C-1′), 70.7 (C-2′), 65.6 (C-3′), 40.3 (3′ NMe_2), 30.5 (C-4′), 69.0 (C-5′), 96.2 (C-1″), 34.9 (C-2″), 72.7 (C-3″), 49.5 (3″ OMe), 77.9 (C-4″), 66.0 (C-5″), 15.3 (2 Me), 9.5 (4 Me), 29 (6 Me), 22.9 (8 Me), 9 (10 Me), 16.7 (12 Me), 21.5 (5′ Me), 21.4 (3″ Me), 18.3 (5″ Me), 49 (α-CH_2); 27.6 (β-CH_2), 38.0 (γ-CH_2), 156.5 (NHCONH), 137.6 (C, b, naphthyl), 120.3 (CH, c, naphthyl), 128.6 (CH, h, naphthyl), 127.4 (CH, e, naphthyl), 123.8 (CH, f, naphthyl), 126.0 (CH, g, naphthyl), 129.0 (CH, a, naphthyl), 114.5 (CH, d, naphthyl), 129.6 (C, j, naphthyl), 134.2 (C, i, naphthyl).

3.3.7. 9-Deoxo-9-dihydro-9a-{N′-[1-(1-naphthyl)ethyl]carbamoyl-γ-aminopropyl}-9a-aza-9a-homoerythromycin A (**4h**)

Yield 49.0%. MS *m*/*z*: (ES): $MH^+ = 989.3$. IR (KBr) [ν/cm^{-1}]: 3414, 2967, 2934, 1728, 1645, 1556, 1459, 1378, 1286, 1167, 1122, 1054, 901, 801, 779. ^{1}H NMR (pyridine-d_5) δ 3.13 (1H, H-2), 4.74 (1H, H-3), 2.51 (1H, H-4), 4.17 (1H, H-5), 1.93; 1.60 (2H, H-7), 1.92 (1H, H-8), 2.76; 2.27 (2H, H-9), 3.09 (1H, H-10), 4.23 (1H, H-11), 5.44 (1H, H-13), 1.71; 2.16 (2H, H-14), 0.93 (3H, H-15), 5.01 (1H, H-1′), 3.63 (1H, H-2′), 2.73 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.40; 1.16 (2H, H-4′), 4.00 (1H, H-5′), 5.22 (1H, H-1″), 2.44; 1.51 (2H, H-2″), 3.51 (3H, 3″ OMe), 3.30 (1H, H-4″), 4.64 (1H, H-5″), 1.35 (3H, 2 Me), 1.60 (3H, 4 Me), 1.74 (3H, 6 Me), 0.94 (1H, H-8 Me), 1.36 (3H, 10 Me), 1.40 (3H, 12 Me), 1.36 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.68 (3H, 5″ Me), 3.27; 2.69 (2H, α-CH_2), 1.89 (2H, β-CH_2), 3.47, 3.39 (2H, γ-CH_2), 6.19 (1H, α″-CH), 1.70 (3H, β″-CH_3), 8.19 (1H, h, naphthyl), 7.82 (1H, e, naphthyl), 7.72 (1H, d, naphthyl), 7.58 (1H, b, naphthyl), 7.53 (1H, g, naphthyl), 7.47 (1H, f, naphthyl), 7.43 (1H, c, naphthyl) 9.18 (1H, NH); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 45.5 (C-2), 79.4 (C-3), 42.0 (C-4), 84.0 (C-5), 74.7 (C-6), 41.9 (C-7), 28.2 (C-8), 63.9 (C-9), 61.6 (C-10), 75.7 (C-11), 75.4 (C-12), 77.9 (C-13), 22.4 (C-14), 11.1 (C-15), 103.6 (C-1′), 71.7 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.5 (C-4′), 68.2 (C-5′), 96.1 (C-1″), 35.5 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.8 (C-4″), 66.2 (C-5″), 15.6 (2 Me), 10.3 (4 Me), 29.0 (6 Me), 22.7 (8 Me), 9.7 (10 Me), 18.4 (12 Me), 22.0 (5′ Me), 21.6 (3″ Me), 19.8 (5″ Me), 49.6 (α-CH_2); 29.2 (β-CH_2), 39.2 (γ-CH_2), 158.5 (NHCONH), 45.8 (α″-CH), 22.6 (β″-CH_3), 131.5 (C, a, naphthyl), 129.3 (CH, b, naphthyl), 127.7 (CH, c, naphthyl), 125.9 (CH, d, naphthyl), 126.5 (CH, e, naphthyl), 122.8 (CH, f, naphthyl), 133.2 (CH, g, naphthyl), 131.6 (CH, h, naphthyl).

3.3.8. 9-Deoxo-9-dihydro-9a-(N′-phenylthiocarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerythromycin A (**6b**)

Yield 43.1%. MS *m*/*z*: (ES): $MH^+ = 927.3$. IR (KBr) [ν/cm^{-1}]: 3440, 2969, 2935, 1728, 1667, 1552, 1456, 1380, 1284, 1167, 1054, 1013, 900, 699. ^{1}H NMR ($CDCl_3$) δ 2.84 (1H, H-2), 3.13 (1H, H-3), 2.00 (1H, H-4), 3.61 (1H, H-5), 2.26; 1.72 (2H, H-7), 2.04 (1H, H-8), 3.73 (1H, H-11), 4.68 (1H, H-13), 1.88; 1.50 (2H, H-14), 0.90 (3H, H-15), 4.44 (1H, H-1′), 3.23 (1H, H-2′), 2.50 (1H, H-3′), 2.32 (6H, 3′ NMe_2), 1.70; 1.24 (2H, H-4′), 3.52 (1H, H-5′), 5.00 (1H, H-1″), 2.33; 1.55 (2H, H-2″), 3.32 (3H, 3″ OMe), 3.02 (1H, H-4″), 4.07 (1H, H-5″), 1.20 (3H, 2 Me), 1.08 (3H, 4 Me), 1.33 (3H, 6 Me), 0.98 (3H, 8 Me), 1.15 (3H, 10 Me), 1.07 (3H, 12 Me), 1.36 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.68 (3H, 5″ Me), 3.3; 2.7 (2H, α-CH_2), 1.87 (2H, β-CH_2), 3.67 (2H, γ-CH_2), 7.38 (2H, phenyl, c), 7.33 (2H, phenyl, b), 7.23 (1H, phenyl, d); ^{13}C NMR ($CDCl_3$) δ 177.8 (C-1), 45.3 (C-2), 79.5 (C-3), 40.4 (C-4), 84.0 (C-5), 74.8 (C-6), 40.7 (C-7), 28.8 (C-8), 64.4 (C-9), 62 (C-10), 74.3 (C-11), 74.6 (C-12), 78.0 (C-13), 21.3 (C-14), 11.2 (C-15), 103.2 (C-1′), 70.9 (C-2′), 65.6 (C-3′), 40.4 (3′ NMe_2), 29.0 (C-4′), 68.9 (C-5′), 96.0 (C-1″), 35.0 (C-2″), 72.8 (C-3″), 49.5 (3″ OMe), 78.0 (C-4″), 65.9 (C-5″), 15.4 (2 Me), 9.7 (4 Me), 26.7 (6 Me), 22.8 (8 Me), 8.4 (10 Me), 16.5 (12 Me), 21.4 (5′ Me), 21.5 (3″ Me), 18.4 (5″ Me), 49.0 (α-CH_2); 27.1 (β-CH_2), 43.4 (γ-CH_2), 181.2 (NHCSNH), 137.3 (phenyl, a), 129.6 (phenyl, c), 126.6 (phenyl, b), 125.3 (phenyl, d).

3.3.9. 9-Deoxo-9-dihydro-9a-(N′-benzylthiocarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerythromycin A (**6c**)

Yield 51.1%. MS *m*/*z*: (ES): $MH^+ = 941.3$. IR (KBr) [ν/cm^{-1}]: 3443, 2969, 2935, 1727, 1667, 1552, 1456, 1380, 1284, 1167, 1054, 1013, 901, 748, 701. ^{1}H NMR (pyridine-d_5 e) δ 3.12 (1H, H-2), 4.74 (1H, H-3), 2.51 (1H, H-4), 4.15 (1H, H-5), 1.93 (2H, H-7), NA (1H, H-8), 2.77; 2.50 (2H, H-9), 3.10 (1H, H-10), 4.20 (1H, H-11), 5.46 (1H, H-13), 1.72; 2.16 (2H, H-14), 0.97 (3H, H-15), 5.05 (1H, H-1′), 3.62 (1H, H-2′), 2.70 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.38; 1.17 (2H, H-4′), 4.00 (1H, H-5′), 5.26 (1H, H-1″), 2.43; 1.53 (2H, H-2″), 3.50 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.64 (1H, H-5″), 1.37 (3H, 2 Me), 1.58 (3H, 4 Me), 1.76 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.39 (3H, 10 Me), 1.40 (3H, 12

Me), 1.36 (3H, 5′ Me), 1.32 (3H, 3″ Me), 1.67 (3H, 5″ Me), 3.3; 2.8 (2H, α-CH_2), 2.06 (2H, β-CH_2), 3.78 (2H, γ-CH_2), 3.8 (2H, α″-CH_2), 7.51 (2H, phenyl, c), 7.30 (2H, phenyl, b), 7.22 (1H, phenyl, d); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 45.5 (C-2), 79.5 (C-3), 41.9 (C-4), 84.0 (C-5), 74.8 (C-6), 41.7 (C-7), 28 (C-8), 64.1 (C-9), 61.4 (C-10), 75.8 (C-11), 75.5 (C-12), 77.9 (C-13), 22.3 (C-14), 11.1 (C-15), 103.5 (C-1′), 71.7 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.7 (C-4′), 68.2 (C-5′), 96.2 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 79.2 (C-4″), 66.2 (C-5″), 15.7 (2 Me), 10.4 (4 Me), 29.0 (6 Me), 22.7 (8 Me), 9.6 (10 Me), 18.4 (12 Me), 23.6 (5′ Me), 21.6 (3″ Me), 19.5 (5″ Me), 49.5 (α-CH_2); 29 (β-CH_2), 43.4 (γ-CH_2), 183 (NHCSNH), 48.3 (α″-CH_2), 133.2 (phenyl, a), 128.6 (phenyl, b), 127.8 (phenyl, c), 127.3 (phenyl, d).

3.3.10. 9-Deoxo-9-dihydro-9a-[N′-(β-phenylethyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**6d**)

Yield 50.1%. MS *m*/*z*: (ES): $MH^+ = 955.3$. IR (KBr) [ν/cm^{-1}]: 3438, 2969, 2935, 1727, 1667, 1552, 1456, 1380, 1284, 1167, 1054, 1013, 901, 748, 701. ^{1}H NMR (pyridine-d_5) δ 3.14 (1H, H-2), 4.75 (1H, H-3), 2.51 (1H, H-4), 4.17 (1H, H-5), 1.93; 1.58 (2H, H-7), 2.24 (1H, H-8), 2.77; 2.28 (2H, H-9), 3.09 (1H, H-10), 4.20 (1H, H-11), 5.42 (1H, H-13), 2.15, 1.69 (2H, H-14), 0.94 (3H, H-15), 4.99 (1H, H-1′), 3.63 (1H, H-2′), 2.73 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.38; 1.17 (2H, H-4′), 4.01 (1H, H-5′), 5.29 (1H, H-1″), 2.43; 1.54 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.30 (1H, H-4″), 4.65 (1H, H-5″), 1.35 (3H, 2 Me), 1.58 (3H, 4 Me), 1.71 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.37 (3H, 10 Me), 1.40 (3H, 12 Me), 1.38 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.67 (3H, 5″ Me), 3.34; 2.76 (2H, α-CH_2), 1.93 (2H, β-CH_2), 4.06 (2H, γ-CH_2), 3.42 (2H, α″-CH_2), 3.17 (2H, β″-CH_2), 7.26 (2H, phenyl, c), 7.28 (2H, phenyl, b), 7.20 (1H, phenyl, d); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 45.5 (C-2), 79.4 (C-3), 42.0 (C-4), 84.1 (C-5), 74.7 (C-6), 42.0 (C-7), 64.3 (C-9), 61.5 (C-10), 75.7 (C-11), 75.3 (C-12), 77.9 (C-13), 22.4 (C-14), 11.3 (C-15), 103.5 (C-1′), 71.7 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.7 (C-4′), 68.2 (C-5′), 96.2 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.8 (C-4″), 66.2 (C-5″), 15.6 (2 Me), 10.4 (4 Me), 28.0 (6 Me), 22.7 (8 Me), 9.7 (10 Me), 18.5 (12 Me), 22.0 (5′ Me), 21.6 (3″ Me), 19.5 (5″ Me), 49.7 (α-CH_2); 28.0 (β-CH_2), 46.2 (γ-CH_2), 183 (NHCSNH), 49.7 (α″-CH_2); 35.6 (β″-CH_2), 140.2 (phenyl, a), 129.3 (phenyl, c), 128.8 (phenyl, b), 126.5 (phenyl, d).

3.3.11. 9-Deoxo-9-dihydro-9a-[N′-(3-phenylpropyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**6e**)

Yield 21.1%. MS *m*/*z*: (ES): $MH^+ = 969.3$. IR (KBr) [ν/cm^{-1}]: 3438, 2969, 2935, 1727, 1667, 1553, 1455, 1380, 1284, 1167, 1054, 1013, 902, 745, 700. ^{1}H NMR (pyridine-d_5) δ 3.14 (1H, H-2), 4.74 (1H, H-3), 2.51 (1H, H-4), 4.16 (1H, H-5), 1.93; 1.58 (2H, H-7), 2.20 (1H, H-8), 2.75; 2.24 (2H, H-9), 3.10 (1H, H-10), 4.20 (1H, H-11), 5.43 (1H, H-13), 2.16, 1.69 (2H, H-14), 0.95 (3H, H-15), 4.99 (1H, H-1′), 3.62 (1H, H-2′), 2.65 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.38; 1.18 (2H, H-4′), 3.99 (1H, H-5′), 5.28 (1H, H-1″), 2.44; 1.53 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.64 (1H, H-5″), 1.35 (3H, 2 Me), 1.60 (3H, 4 Me), 1.74 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.38 (3H, 10 Me), 1.40 (3H, 12 Me), 1.36 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.68 (3H, 5″ Me), 3.30; 2.78 (2H, α-CH_2), 2.04 (2H, β-CH_2), 3.81 (2H, γ-CH_2), 3.81 (2H, α″-CH_2), 2.04 (2H, β″-CH_2), 2.67 (2H, γ″-CH_2), 7.27 (2H, phenyl, c), 7.18 (1H, phenyl, d), 7.23 (2H, phenyl, b); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 45.5 (C-2), 79.4 (C-3), 41.9 (C-4), 84.1 (C-5), 74.7 (C-6), 41.8 (C-7), 28 (C-8), 64 (C-9), 61.5 (C-10), 75.8 (C-11), 75.3 (C-12), 77.9 (C-13), 22.4 (C-14), 11.1 (C-15), 103.5 (C-1′), 71.7 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.7 (C-4′), 68.3 (C-5′), 96.2 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.8 (C-4″), 66.2 (C-5″), 15.6 (2 Me), 10.4 (4 Me), 29.0 (6 Me), 22.7 (8 Me), 9.7 (10 Me), 18.4 (12 Me), 22.0 (5′ Me), 21.6 (3″ Me), 19.5 (5″ Me), 48 (α-CH_2); 29.2 (β-CH_2), 43.4 (γ-CH_2), 183 (NHCSNH), 44.3 (α″-CH_2), 31.5 (β″-CH_2), 33.5 (γ″-CH_2), 133.2 (phenyl, a), 128.8 (phenyl, b), 128.7 (phenyl, c), 126.2 (phenyl, d).

3.3.12. 9-Deoxo-9-dihydro-9a-[N′-(1-naphthyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**6f**)

Yield 35.1%. MS *m*/*z*: (ES): $MH^+ = 977.3$. IR (KBr) [ν/cm^{-1}]: 3424, 2964, 2933, 1728, 1537, 1460, 1378, 1280, 1166, 1052, 1014, 902, 794, 794. ^{1}H NMR (pyridine-d_5) δ 3.11 (1H, H-2), 4.74 (1H, H-3), 2.49 (1H, H-4), 4.14 (1H, H-5), 1.96; 1.88 (2H, H-7), 1.71 (1H, H-8), 2.76; 2.30 (2H, H-9), 3.08 (1H, H-10), 4.18 (1H, H-11), 5.39 (1H, H-13), 1.72; 2.10 (2H, H-14), 0.91 (3H, H-15), 4.98 (1H, H-1′), 3.63 (1H, H-2′), 2.71 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.38; 1.18 (2H, H-4′), 4.01 (1H, H-5′), 5.29 (1H, H-1″), 2.43; 1.50 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.30 (1H, H-4″), 4.64 (1H, H-5″), 1.35 (3H, 2 Me), 1.58 (3H, 4 Me), 1.27 (3H, 6 Me), 0.95 (1H, H-8 Me), 1.38 (3H, 10 Me), 1.38 (3H, 12 Me), 1.26 (3H, 5′ Me), 1.32 (3H, 3″ Me), 1.68 (3H, 5″ Me), 3.26; 2.83 (2H, α-CH_2), 2.19 (2H, β-CH_2), 3.87 (2H, γ-CH_2), 7.53 (1H, c, naphthyl), 7.91 (1H, d, naphthyl), 7.80 (1H, e, naphthyl), 7.64 (1H, h, naphthyl), 7.49 (1H, f, naphthyl), 7.38 (1H, g, naphthyl),8.40 (1H, b, naphthyl); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 45.5 (C-2), 79.1 (C-3), 42.2 (C-4), 84.0 (C-5), 74.6 (C-6), 42.1 (C-7), 28.1 (C-8), 64.4 (C-9), 61.5 (C-10), 75.4 (C-11), 75.3 (C-12), 77.8 (C-13), 22.4 (C-14), 11.1 (C-15), 103.5 (C-1′), 71.7 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.7 (C-4′), 68.2 (C-5′), 96.0 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 79.0 (C-4″), 66.2 (C-5″), 15.5 (2 Me), 10.3 (4 Me), 28.9 (6 Me), 22.8 (8 Me), 10.0 (10 Me), 18.4 (12 Me), 22.0 (5″ Me), 21.6 (3″ Me), 19.3 (5″ Me), 48.8 (α-CH_2); 29.2 (β-CH_2), 44.1 (γ-CH_2), 183.3 (NHCSNH), 133.1 (C, c, naphthyl), 129.3 (CH, d, naphthyl), 128.6 (CH, e, naphthyl), 126.8 (CH, f, naphthyl), 126.3 (CH, g, naphthyl), 125.6 (CH, h, naphthyl), 123.2 (CH, b, naphthyl), 131.5 (CH, c, naphthyl), 131.1 (C, j, naphthyl), 135.1 (C, i, naphthyl).

3.3.13. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-isopropylcarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**8a**)

Yield 30.5%. MS *m*/*z*: (ES): $MH^+ = 930.2$. IR (KBr) [ν/cm^{-1}]: 3435, 2972, 2936, 2877, 2249, 1726, 1637, 1529, 1459, 1377, 1168, 1053, 1013. ^{1}H NMR (pyridine-d_5) δ 3.16 (1H, H-2), 4.69 (1H, H-3), 2.51 (1H, H-4), 4.15 (1H, H-5), 2.05; 1.87 (2H, H-7), 2.21 (1H, H-8), 2.74; 2.28 (2H, H-9), 3.10 (1H, H-10), 4.20 (1H, H-11), 5.37 (1H, H-13), 2.17; 1.70 (2H, H-14), 0.94 (3H, H-15), 5.00 (1H, H-1′), 3.62 (1H, H-2′), 2.69 (1H, H-3′), 2.17 (6H, 3′ NMe_2), 1.40; 1.16 (2H, H-4′), 4.03 (1H, H-5′), 5.26 (1H, H-1″), 2.45; 1.53 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.32 (1H, H-4″), 4.65 (1H, H-5″), 1.35 (3H, 2 Me), 1.62 (3H, 4 Me), 1.78 (3H, 6 Me), 0.99 (1H, H-8 Me), 1.35 (3H, 10 Me), 1.40 (3H, 12 Me), 1.36 (3H, 5′ Me), 1.33 (3H, 3″ Me), 1.69 (3H, 5″ Me), 3.26; 2.51 (2H, α-CH_2), 1.97 (2H, β-CH_2), 3.56; 3.41 (2H, γ-CH_2), 3.83; 2.71 (2H, α′-CH_2), 2.93 (2H, β′-CH_2), 4.33 (1H, CH, a), 1.19 (3H, CH_3, b); ^{13}C NMR (pyridine-d_5) δ 177.7 (C-1), 45.5 (C-2), 79.3 (C-3), 41.5 (C-4), 83.8 (C-5), 74.7 (C-6), 41.2 (C-7), 29.1 (C-8), 63.7 (C-9), 60.5 (C-10), 75.9 (C-11), 75.3 (C-12), 78.1 (C-13), 22.0 (C-14), 11.5 (C-15), 103.5 (C-1′), 71.7 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.4 (C-4′), 68.2 (C-5′), 96.2 (C-1″), 35.6 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.8 (C-4″), 66.2 (C-5″), 15.8 (2 Me), 10.3 (4 Me), 28.1 (6 Me), 23.3 (8 Me), 8.8 (10 Me), 18.3 (12 Me), 22.0 (5′ Me), 21.4 (3″ Me), 19.5 (5″ Me), 48.9 (α-CH_2), 27.4 (β-CH_2), 46.5 (γ-CH_2), 43.7 (α′-CH_2), 17.5 (β′-CH_2), 119.7 (CN), 157.5 (NCONH), 42.9 (CH, isopropyl, a), 23.7 (CH_3, isopropyl, b).

3.3.14. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-phenylcarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**8b**)

Yield 35.5%. MS *m*/*z*: (ES): $MH^+ = 964.3$. IR (KBr) [ν/cm^{-1}]: 3450, 2972, 2938, 2877, 2249, 1728, 1650, 1534, 1447, 1378, 1315, 1167, 1053, 1013, 897, 755, ^{1}H NMR ($CDCl_3$) δ 2.89 (1H, H-2), 4.11 (1H, H-3), 2.03 (1H, H-4), 3.62 (1H, H-5), 1.79; 1.33 (2H, H-7), 2.1 (1H, H-8), 3.00; 2.18 (2H, H-9), 2.86 (1H, H-10), 3.76 (1H, H-11), 4.65 (1H, H-13), 1.89; 1.51 (2H, H-14), 0.89 (3H, H-15), 4.44 (1H, H-1′), 3.24 (1H, H-2′), 2.49 (1H, H-3′), 2.32 (6H, 3′ NMe_2), 1.69; 1.22 (2H, H-4′), 3.48 (1H, H-5′), 4.97

(1H, H-1″), 2.35; 1.57 (2H, H-2″), 3.32 (3H, 3″ OMe), 3.01 (1H, H-4″), 4.04 (1H, H-5″), 1.20 (3H, 2 Me), 1.09 (3H.4 Me), 1.33 (3H, 6 Me), 1.00 (1H, 8 Me), 1.11 (3H, 10 Me), 1.07 (3H, 12 Me), 1.21 (3H, 5′ Me), 1.24 (3H, 3″ Me), 1.31 (3H, 5″ Me), 3.32 (2H, α-CH_2), 2.54 (2H, β-CH_2), 3.25; 2.89 (2H, γ-CH_2), 3.68; 2.87 (2H, α′-CH_2), 2.80 (2H, β′-CH_2), 7.40 (2H, phenyl, b), 7.27 (2H, phenyl, c), 7.03 (1H, phenyl, d); ^{13}C NMR ($CDCl_3$) δ 178.1 (C-1), 44.9 (C-2), 79.8 (C-3), 40.1 (C-4), 83.4 (C-5), 74.7 (C-6), 39.7 (C-7), 29.0 (C-8), 63 (C-9), 74.7 (C-12), 77.9 (C-13), 21.1 (C-14), 11.1 (C-15), 102.9 (C-1′), 70.9 (C-2′), 65.7 (C-3′), 40.4 (3′ NMe_2), 29.0 (C-4′), 68.8 (C-5′), 96.0 (C-1″), 35.0 (C-2″), 72.8 (C-3″), 49.4 (3″ OMe), 77.9 (C-4″), 65.9 (C-5″), 15.5 (2 Me), 9.5 (4 Me), 27.0 (6 Me), 23.3 (8 Me), 7.4 (10 Me), 16.3 (12 Me), 21.4 (5′ Me), 21.5 (3″ Me), 18.4 (5″ Me), 47.6 (α-CH_2), 27.3 (β-CH_2), 48.9 (γ-CH_2), 44.4 (α′-CH_2), 17.3 (β″-CH_2), 119.2 (CN), 155.3 (NCONH), 138.9 (phenyl, a), 128.7 (phenyl, c), 123.3 (phenyl, d), 121.0 (phenyl, b).

3.3.15. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-benzylcarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**8c**)

Yield 34.1%. MS *m*/*z*: (ES): $MH^+ = 978.3$. IR (KBr) [ν/cm^{-1}]: 3417, 2971, 2936, 2876, 2248, 1694, 1644, 1538, 1455, 1377, 1267, 1167, 1053, 1012, 900, 732, 700. ^{1}H NMR ($CDCl_3$) δ 2.89 (1H, H-2), 4.10 (1H, H-3), 2.05 (1H, H-4), 3.62 (1H, H-5), 1.79, 1.41 (2H, H-7), 2.05 (1H, H-8), NA (2H, H-9), NA (1H, H-10), 3.73 (1H, H-11), 4.57 (1H, H-13), 1.88; 1.46 (2H, H-14), 0.89 (3H, H-15), 4.45 (1H, H-1′), 3.22 (1H, H-2′), 2.66 (1H, H-3′), 2.33 (6H, 3′ NMe_2), NA (2H, H-4′), 3.53 (1H, H-5′), 4.76 (1H, H-1″), 2.28; 1.52 (2H, H-2″), 3.30 (3H, 3″ OMe), 3.01 (1H, H-4″), 4.05 (1H, H-5″), 1.21 (3H, 2 Me), 1.08 (3H, 4 Me), 1.31 (3H, 6 Me), 1.01 (1H, 8 Me), 1.05 (3H, 10 Me), 1.11 (3H, 12 Me), 1.22 (3H, 5′ Me), 1.24 (3H, 3″ Me), 1.22 (3H, 5″ Me), 3.32; 2.85 (2H, α-CH_2), 1.70 (2H, β-CH_2), 3.25 (2H, γ-CH_2), 3.55 (2H, α′-CH_2), 2.69 (2H, β′-CH_2), 4.40 (2H, α″-CH_2), 7.33 (2H, phenyl, b), 7.29 (2H, phenyl, c), 7.14 (1H, phenyl, d); ^{13}C NMR ($CDCl_3$) δ 177 (C-1), 44.8 (C-2), 79 (C-3), 39.3 (C-4), 83 (C-5), 74.8 (C-6), 39.2 (C-7), 28.9 (C-8), 63 (C-9), 60 (C-10), 74.6 (C-11), 74.6 (C-12), 78 (C-13), 21.3 (C-14), 11.2 (C-15), 102.9 (C-1′), 71.0 (C-2′), 65.6 (C-3′), 39.3 (3′ NMe_2), 28.9 (C-4′), 68.7 (C-5′), 96.4 (C-1″), 35.2 (C-2″), 72.7 (C-3″), 50.3 (3″ OMe), 77.8 (C-4″), 66.0 (C-5″), 15.7 (2 Me), 9.6 (4 Me), 26.9 (6 Me), 23.8 (8 Me), 6.8 (10 Me), 16.1 (12 Me), 21.4 (5′ Me), 21.5 (3″ Me), 18.6 (5″ Me), 50.3 (α-CH_2); 27.3 (β-CH_2), 48.3 (γ-CH_2), 44.3 (α′-CH_2); 17.2 (β″-CH_2), 157.5 (NHCONH), 119 (CN), 44.7 (α″-CH_2), 140.3(phenyl, a), 129.3 (phenyl, b), 128.7 (phenyl, c), 127.5 (phenyl, d).

3.3.16. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-phenylethylcarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**8d**)

Yield 30.1%. MS *m*/*z*: (ES): $MH^+ = 992.3$. IR (KBr) [ν/cm^{-1}]: 3444, 2971, 2936, 2876, 2249, 1694, 1644, 1538, 1455, 1377, 1267, 1167, 1053, 1012, 700. ^{1}H NMR ($CDCl_3$) δ 2.89 (1H, H-2), 4.05 (1H, H-3), 2.02 (1H, H-4), 3.61 (1H, H-5), 1.81, 1.37 (2H, H-7), 2.03 (1H, H-8), 2.83, 2.33 (2H, H-9), 2.71 (1H, H-10), 3.70 (1H, H-11), 4.60 (1H, H-13), 1.88; 1.51 (2H, H-14), 0.89 (3H, H-15), 4.44 (1H, H-1′), 3.23 (1H, H-2′), 2.48 (1H, H-3′), 2.31 (6H, 3′ NMe_2), 1.69, 1.23 (2H, H-4′), 3.46 (1H, H-5′), 4.94 (1H, H-1″), 2.32; 1.56 (2H, H-2″), 3.31 (3H, 3″ OMe), 2.99 (1H, H-4″), 4.03 (1H, H-5″), 1.22 (3H, 2 Me), 1.09 (3H, 4 Me), 1.31 (3H, 6 Me), 0.99 (1H, H-8 Me), 1.08 (3H, 10 Me), 1.06 (3H, 12 Me), 1.21 (3H, 5′ Me), 1.23 (3H, 3″ Me), 1.24 (3H, 5″ Me), 3.2; 2.8 (2H, α-CH_2), 1.86 (2H, β-CH_2), 3.05 (2H, γ-CH_2), 3.60, 3.50 (2H, α′-CH_2), 2.67 (2H, β′-CH_2), 3.48 (2H, α″-CH_2), 2.84 (2H, β″-CH_2), 7.28 (2H, phenyl, b), 7.21 (2H, phenyl, c), 7.20 (1H, phenyl, d); ^{13}C NMR ($CDCl_3$) δ 178.1 (C-1), 44.9 (C-2), 80.2 (C-3), 40.0 (C-4), 83.5 (C-5), 74.7 (C-6), 39.5 (C-7), 28.9 (C-8), 63.4 (C-9), 60 (C-10), 74.4 (C-11), 74.6 (C-12), 78.3 (C-13), 21.1 (C-14), 11.1 (C-15), 102.9 (C-1′), 70.9 (C-2′), 65.7 (C-3′), 40.4 (3′ NMe_2), 28.9 (C-4′), 68.8 (C-5′), 96.1 (C-1″), 35.1 (C-2″), 72.8 (C-3″), 49.4 (3″ OMe), 77.9 (C-4″), 65.9 (C-5″), 15.5 (2 Me), 9.5 (4 Me), 27.1 (6 Me), 23.4 (8 Me), 7.2 (10 Me), 16.2 (12 Me), 21.4 (5′ Me), 21.5 (3″ Me), 18.5 (5″ Me), 49.0 (α-CH_2); 27.0 (β-CH_2), 47.4 (γ-CH_2), 44.4 (α′-CH_2); 17.4 (β′-CH_2), 157.4 (NHCONH), 119.1 (CN), 42.1 (α″-CH_2), 36.5 (β″-CH_2), 139.6 (phenyl, a), 129.0 (phenyl, c), 128.4 (phenyl, b), 126.2 (phenyl, d).

3.3.17. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-(1-naphthyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**8f**)

Yield 36.1%. MS *m*/*z*: (ES): $MH^+ = 1014.3$. IR (KBr) [ν/cm^{-1}]: 3439, 2972, 2937, 2249, 1727, 1642, 1528, 1501, 1460, 1377, 1168, 1053, 1013, 794, 773. ^{1}H NMR ($CDCl_3$) δ 2.86 (1H, H-2), 3.94 (1H, H-3), 2.02 (1H, H-4), 3.54 (1H, H-5), 1.78, 1.37 (2H, H-7), 2.10 (1H, H-8), 2.82; 2.31 (2H, H-9), 2.86 (1H, H-10), 3.75 (1H, H-11), 4.63 (1H, H-13), 1.88; 1.49 (2H, H-14), 0.89 (3H, H-15), 4.40 (1H, H-1′), 3.23 (1H, H-2′), 2.44 (1H, H-3′), 2.31 (6H, 3′ NMe_2), 1.69; 1.25 (2H, H-4′), 3.44 (1H, H-5′), 4.74 (1H, H-1″), 2.31; 1.50 (2H, H-2″), 3.28 (3H, 3″ OMe), 3.06 (1H, H-4″), 3.95 (1H, H-5″), 1.19 (3H, 2 Me), 1.07 (3H, 4 Me), 1.31 (3H, 6 Me), 0.99 (1H, H-8 Me), 1.14 (3H, 10 Me), 1.08 (3H, 12 Me), 1.20 (3H, 5′ Me), 1.20 (3H, 3″ Me), 1.28 (3H, 5″ Me), 2.41; 2.86 (2H, α-CH_2), 1.94 (2H, β-CH_2), 3.58; 3.41 (2H, γ-CH_2), 3.73 (2H, α′-CH_2), 2.79 (2H, β′-CH_2), 7.91 (1H, e, naphthyl), 7.83 (1H, h, naphthyl), 7.68 (1H, b, naphthyl), 7.60 (1H, d, naphthyl), 7.50 (1H, f, naphthyl), 7.47 (1H, g, naphthyl), 7.43 (1H, c, naphthyl); ^{13}C NMR ($CDCl_3$) δ 178.0 (C-1), 44.8 (C-2), 79.9 (C-3), 40.0 (C-4), 83.6 (C-5), 74.6 (C-6), 39.7 (C-7), 29.3 (C-8), 63 (C-9), 60 (C-10), 74.7 (C-11), 74.6 (C-12), 78.2 (C-13), 21.0 (C-14), 11.1 (C-15), 102.9 (C-1′), 70.9 (C-2′), 65.6 (C-3′), 40.3 (3′ NMe_2), 29.0 (C-4′), 68.7 (C-5′), 95.8 (C-1″), 34.8 (C-2″), 72.7 (C-3″), 49.4 (3″ OMe), 77.8 (C-4″), 65.6 (C-5″), 15.5 (2 Me), 9.4 (4 Me), 27.1 (6 Me), 23.3 (8 Me), 7.3 (10 Me), 16.2 (12 Me), 21.5 (5′ Me), 21.4 (3″ Me), 18.3 (5″ Me), 49.3 (α-CH_2); 27.7 (β-CH_2), 47.8 (γ-CH_2), 44.4 (α′-CH_2); 17.2 (β″-CH_2), 156.3 (NHCONH), 119.1 (CN), 134.3 (C, a, naphthyl), 134.0 (C, i, naphthyl), 129.4 (CH, c, naphthyl), 128.4 (CH, h, naphthyl), 125.7 (CH, b, naphthyl), 125.8 (CH, f, naphthyl), 125.8 (CH, c, naphthyl), 126.2 (CH, g, naphthyl), 122.8 (CH, d, naphthyl), 122.1 (CH, e, naphthyl).

3.3.18. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-(2-naphthyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**8g**)

Yield 33.1%. MS *m*/*z*: (ES): $MH^+ = 1014.3$. IR (KBr) [ν/cm^{-1}]: 3444, 2972, 2937, 2249, 1712, 1650, 1543, 1503, 1456, 1377, 1167, 1053, 1013, 749. ^{1}H NMR ($CDCl_3$) δ 2.91 (1H, H-2), 4.09 (1H, H-3), 2.04 (1H, H-4), 3.61 (1H, H-5), 1.78, 1.37 (2H, H-7), 2.05 (1H, H-8), NA (2H, H-9), NA (1H, H-10), 3.77 (1H, H-11), 4.64 (1H, H-13), 1.88; 1.49 (2H, H-14), 0.89 (3H, H-15), 4.89 (1H, H-1′), 3.23 (1H, H-2′), 2.46 (1H, H-3′), 2.30 (6H, 3′ NMe_2), 1.67; 1.21 (2H, H-4′), 3.47 (1H, H-5′), 4.43 (1H, H-1″), 2.30; 1.48 (2H, H-2″), 3.31 (3H, 3″ OMe), 2.91 (1H, H-4″), 4.01 (1H, H-5″), 1.19 (3H, 2 Me), 1.08 (3H, 4 Me), 1.34 (3H, 6 Me), 1.01 (1H, H-8 Me), 1.12 (3H, 10 Me), 1.20 (3H, 12 Me), 1.20 (3H, 5′ Me), 1.19 (3H, 3″ Me), 1.31 (3H, 5″ Me), NA (2H, α-CH_2), 1.89 (2H, β-CH_2), 3.5 (2H, γ-CH_2), 3.74 (2H, α′-CH_2), 2.82 (2H, β′-CH_2), 7.96 (1H, h, naphthyl), 7.75 (1H, c, naphthyl), 7.74 (1H, d, naphthyl), 7.74 (1H, g, naphthyl), 7.49 (1H, a, naphthyl), 7.41 (1H, f, naphthyl), 7.35 (1H, e, naphthyl); ^{13}C NMR ($CDCl_3$) δ 177 (C-1), 44.3 (C-2), 79.4 (C-3), 39.7 (C-4), 83.0 (C-5), 73.9 (C-6), 39.3 (C-7), 28.5 (C-8), 62.7 (C-9), 60 (C-10), 74.1 (C-11), 74.0 (C-12), 77.8 (C-13), 20.5 (C-14), 10.4 (C-15), 102.4 (C-1′), 70.1 (C-2′), 64.8 (C-3′), 39.7 (3′ NMe_2), 28.3 (C-4′), 68.3 (C-5′), 95.4 (C-1″), 34.4 (C-2″), 72.1 (C-3″), 48.8 (3″ OMe), 77.1 (C-4″), 65.0 (C-5″), 15.0 (2 Me), 8.93 (4 Me), 26.4 (6 Me), 23.2 (8 Me), 6.66 (10 Me), 15.8 (12 Me), 20.9 (5″ Me), 20.6 (3″ Me), 17.8 (5″ Me), 48.4 (α-CH_2); 26.8 (β-CH_2), 47.0 (γ-CH_2), 43.7 (α′-CH_2); 16.7 (β″-CH_2), 154.9 (NHCONH), 118.6 (CN), 135.9 (CH, a, naphthyl), 120.9 (CH, b, naphthyl), 127.8 (CH, c, naphthyl), 126.7 (CH, d, naphthyl), 123.9 (CH, e, naphthyl), 125.5

(CH, f, naphthyl), 116.6 (CH, h, naphthyl), 133.4 (C, i, naphthyl), 129.7 (C, j, naphthyl).

3.3.19. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-[1-(1-naphthyl)ethyl]carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**8h**)

Yield 30.0%. MS *m*/*z*: (ES): $MH^+ = 1042.4$. IR (KBr) [ν/cm^{-1}]: 3444, 2972, 2936, 1728, 1634, 1520, 1456, 1377, 1168, 1053, 1013, 801, 779. ^{1}H NMR ($CDCl_3$) δ 2.86 (1H, H-2), 4.11 (1H, H-3), 2.01 (1H, H-4), 3.60 (1H, H-5), 1.76, 1.38 (2H, H-7), 1.99 (1H, H-8), 2.66; 2.12 (2H, H-9), 2.74 (1H, H-10), 3.67 (1H, H-11), 4.59 (1H, H-13), 1.88; 1.49 (2H, H-14), 0.92 (3H, H-15), 4.44 (1H, H-1′), 3.23 (1H, H-2′), 2.47 (1H, H-3′), 2.30 (6H, 3′ NMe_2), 1.69; 1.31 (2H, H-4′), 3.51 (1H, H-5′), 5.00 (1H, H-1″), 2.36; 1.59 (2H, H-2″), 3.31 (3H, 3″ OMe), 3.03 (1H, H-4″), 4.06 (1H, H-5″), 1.23 (3H, 2 Me), 1.08 (3H, 4 Me), 1.68 (3H, 6 Me), 0.98 (1H, 8 Me), 1.04 (3H, 10 Me), 1.32 (3H, 12 Me), 1.24 (3H, 5′ Me), 1.25 (3H, 3″ Me), 1.30 (3H, 5″ Me), 3.02; 2.30 (2H, α-CH_2), 1.88 (2H, β-CH_2), 3.20 (2H, γ-CH_2), 3.59 (2H, α′-CH_2), 2.72 (2H, β′-CH_2), 5.80; 5.03 (2H, α″-CH_2), 1.68 (3H, β″-CH_2), 8.15 (1H, b, naphthyl), 7.85 (1H, d, naphthyl), 7.76 (1H, e, naphthyl), 7.54 (1H, h, naphthyl), 7.52 (1H, c, naphthyl), 7.48 (1H, g, naphthyl), 7.45 (1H, f, naphthyl); ^{13}C NMR ($CDCl_3$) δ 177.4 (C-1), 44.2 (C-2), 79.9 (C-3), 39.6 (C-4), 82.9 (C-5), 73.8 (C-6), 39.4 (C-7), 28.2 (C-8), 63.2 (C-9), 60 (C-10), 77.4 (C-11), 74.0 (C-12), 78.9 (C-13), 20.6 (C-14), 10.8 (C-15), 102.3 (C-1′), 70.3 (C-2′), 65.1 (C-3′), 40.4 (3′ NMe_2), 29.8 (C-4′), 68.1 (C-5′), 95.1 (C-1″), 34.4 (C-2″), 72.2 (C-3″), 48.7 (3″ OMe), 78.9 (C-4″), 65.2 (C-5″), 13.5 (2 Me), 9.0 (4 Me), 26.5 (6 Me), 22.4 (8 Me), 6.9 (10 Me), 14.9 (12 Me), 21.8 (5″ Me), 21.2 (3″ Me), 16.5 (5″ Me), 49.4 (α-CH_2); 26.8 (β-CH_2), 48 (γ-CH_2), 43 (α″-CH_2); 17.0 (β″-CH_2), 158 (NHCONH), 118.7 (CN), 46.0 (α″-CH_2), 21.8 (β″-CH_2), 139.1 (C, a, naphthyl), 133.4 (C, i, naphthyl), 130, 5 (C, j, naphthyl), 128.1 (CH, d, naphthyl), 127.3 (CH, e, naphthyl), 125.7 (CH, c, naphthyl), 125.1 (CH, g, naphthyl), 124.3 (CH, f, naphthyl), 122.9 (CH, b, naphthyl), 121.6 (CH, h, naphthyl).

3.3.20. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-phenylthiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**10b**)

Yield 30.0%. MS *m*/*z*: (ES): $MH^+ = 980.3$. IR (KBr) [ν/cm^{-1}]: 450, 2972, 2937, 2877, 2249, 1726, 1522, 1456, 1375, 1167, 1053, 1013, 900, 701. ^{1}H NMR ($CDCl_3$) δ 2.90 (1H, H-2), 4.05 (1H, H-3), 2.01 (1H, H-4), 3.59 (1H, H-5), 1.79; 1.32 (2H, H-7), 2.07 (1H, H-8), 2.78; 2.1 (2H, H-9), 2.88 (1H, H-10), 3.73 (1H, H-11), 4.64 (1H, H-13), 1.89; 1.49 (2H, H-14), 0.88 (3H, H-15), 4.45 (1H, H-1′), 3.25 (1H, H-2′), 2.51 (1H, H-3′), 2.33 (6H, 3′ NMe_2), 1.72; 1.22 (2H, H-4′), 3.50 (1H, H-5′), 4.95 (1H, H-1″), 2.32; 1.58 (2H, H-2″), 3.31 (3H, 3″ OMe), 3.02 (1H, H-4″), 4.05 (1H, H-5″), 1.21 (3H, 2 Me), 1.07 (3H, 4 Me), 1.28 (3H, 6 Me), 0.99 (1H, H-8 Me), 1.14 (3H, 10 Me), 1.08 (3H, 12 Me), 1.21 (3H, 5′ Me), 1.24 (3H, 3″ Me), 1.25 (3H, 5″ Me), 3.02 (2H, α-CH_2), 2.23 (2H, β-CH_2), 3.51; 2.8 (2H, γ-CH_2), 4.27; 4.15 (2H, α′-CH_2), 3.02 (2H, β′-CH_2), 7.33 (2H, phenyl, b), 7.34 (2H, phenyl, c), 7.22 (1H, phenyl, d). ^{13}C NMR ($CDCl_3$) δ 178.1 (C-1), 44.9 (C-2), 80.2 (C-3), 40.0 (C-4), 83.6 (C-5), 74.8 (C-6), 39.7 (C-7), 29.3 (C-8), 65 (C-9), 74.7 (C-11), 74.6 (C-12), 78.2 (C-13), 21.0 (C-14), 11.1 (C-15), 103.0 (C-1′), 70.9 (C-2′), 65.7 (C-3′), 40.4 (3′ NMe_2), 28.9 (C-4′), 68.8 (C-5′), 96.0 (C-1″), 35.1 (C-2″), 72.8 (C-3″), 49.4 (3″ OMe), 77.8 (C-4″), 66.0 (C-5″), 15.6 (2 Me), 9.5 (4 Me), 27.0 (6 Me), 23.2 (8 Me), 7.3 (10 Me), 16.2 (12 Me), 21.4 (5′ Me), 21.5 (3″ Me), 18.6 (5″ Me), 49.2 (α-CH_2), 26.2 (β-CH_2), 50.2 (γ-CH_2), 49.3 (α′-CH_2), 16.4 (β′-CH_2), 119.0 (CN), 182.4 (NCONH), 139.9 (phenyl, a), 128.7 (phenyl, b), 127.1 (phenyl, c), 126.3 (phenyl, d).

3.3.21. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-benzylthiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**10c**)

Yield 44.0%. MS *m*/*z*: (ES): $MH^+ = 994.4$. IR (KBr) [ν/cm^{-1}]: 3444, 2972, 2937, 2877, 2249, 1721, 1531, 1455, 1379, 1167, 1053, 1012, 896, 699. ^{1}H NMR ($CDCl_3$) δ 2.89 (1H, H-2), 4.16 (1H, H-3), 2.18 (1H, H-4), 3.63 (1H, H-5), 1.80; 1.33 (2H, H-7), 2.05 (1H, H-8), 2.78; 2.20 (2H, H-9), 2.85 (1H, H-10), 3.73 (1H, H-11), 4.62 (1H, H-13), 1.89; 1.50 (2H, H-14), 0.90 (3H, H-15), 4.45 (1H, H-1′), 3.24 (1H, H-2′), 2.48 (1H, H-3′), 2.32 (6H, 3′ NMe_2), 1.69; 1.24 (2H, H-4′), 3.50 (1H, H-5′), 4.98 (1H, H-1″), 2.37; 1.59 (2H, H-2″), 3.33 (3H, 3″ OMe), 3.02 (1H, H-4″), 4.10 (1H, H-5″), 1.19 (3H, 2 Me), 1.09 (3H, 4 Me), 1.33 (3H, 6 Me), 0.99 (1H, H-8 Me), 1.11 (3H, 10 Me), 1.08 (3H, 12 Me), 1.23 (3H, 5′ Me), 1.25 (3H, 3″ Me), 1.31 (3H, 5″ Me), 3.12, 2.46 (2H, α-CH_2), 2.78 (2H, β-CH_2), 4.08; 3.82 (2H, γ-CH_2), 4.23 (2H, α′-CH_2), 2.87 (2H, β′-CH_2), 7.30 (2H, phenyl, b), 7.27 (2H, phenyl, c), 7.19 (1H, phenyl, d), 5.78 (2H, α‴-CH_2). ^{13}C NMR ($CDCl_3$) δ 178.3 (C-1), 44.9 (C-2), 79.5 (C-3), 40.4 (C-4), 83.3 (C-5), 74.3 (C-6), 40.1 (C-7), 28.8 (C-8), 63.2 (C-9), 59.6 (c-10), 74.2 (C-11), 74.6 (C-12), 78.2 (C-13), 21.2 (C-14), 11.2 (C-15), 102.9 (C-1′), 70.9 (C-2′), 65.7 (C-3′), 40.4 (3′ NMe_2), 28.9 (C-4′), 68.7 (C-5′), 95.8 (C-1″), 35.0 (C-2″), 72.8 (C-3″), 49.4 (3″ OMe), 78.0 (C-4″), 65.7 (C-5″), 15.4 (2 Me), 9.4 (4 Me), 27.2 (6 Me), 23.4 (8 Me), 7.7 (10 Me), 16.3 (12 Me), 21.4 (5′ Me), 21.5 (3″ Me), 18.5 (5″ Me), 48.1 (α-CH_2), 26.4 (β-CH_2), 55.0 (γ-CH_2), 49.2 (α′-CH_2), 16.5 (β′-CH_2), 119.0 (CN), 180.8 (NCSNH), 138.1 (phenyl, a), 128.3 (phenyl, c), 126.9 (phenyl, b), 126.7 (phenyl, d).

3.3.22. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-(β-phenylethyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**10d**)

Yield 36.0%. MS *m*/*z*: (ES): $MH^+ = 1008.4$. IR (KBr) [ν/cm^{-1}]: 3444, 2972, 2936, 2250, 1727, 1530, 1455, 1380, 1169, 1053, 1012, 896, 701. ^{1}H NMR ($CDCl_3$) δ 2.91 (1H, H-2), 4.01 (1H, H-3), 2.02 (1H, H-4), 3.62 (1H, H-5), 1.82, 1.33 (2H, H-7), 2.27 (1H, H-8), 3.69 (1H, H-11), 4.58 (1H, H-13), 1.89; 1.48 (2H, H-14), 0.89 (3H, H-15), 4.45 (1H, H-1′), 3.23 (1H, H-2′), 2.47 (1H, H-3′), 2.31 (6H, 3′ NMe_2), 1.69; 1.25 (2H, H-4′), 3.49 (1H, H-5′), 4.90 (1H, H-1″), 2.32; 1.56 (2H, H-2″), 3.30 (3H, 3″ OMe), 2.97 (1H, H-4″), 3.99 (1H, H-5″), 1.19 (3H, 2 Me), 1.10 (3H, 4 Me), 1.33 (3H, 6 Me), 1.01 (1H, H-8 Me), 1.08 (3H, 10 Me), 1.06 (3H, 12 Me), 1.16 (3H, 5′ Me), 1.23 (3H, 3″ Me), 1.21 (3H, 5″ Me), 3.44, 3.27 (2H, α-CH_2), 2.19 (2H, β-CH_2), 3.96; 3.94 (2H, α′-CH_2), 2.98, 2.88 (2H, β′-CH_2), 3.98, 3.86 (2H, α″-CH_2); 2.90 (2H, β″-CH_2), 7.30 (phenyl, b), 7.26 (phenyl, c), 7.19 (phenyl, d); ^{13}C NMR ($CDCl_3$) δ 178.0 (C-1), 44.8 (C-2), 80.8 (C-3), 39.5 (C-4), 83.5 (C-5), 74.6 (C-6), 38.8 (C-7), 28.8 (C-8), 74.9 (C-11), 74.9 (C-12), 78.4 (C-13), 21.0 (C-14), 11.1 (C-15), 102.9 (C-1′), 71.0 (C-2′), 65.6 (C-3′), 40.3 (3′ NMe_2), 28.9 (C-4′), 68.7 (C-5′), 96.4 (C-1″), 35.1 (C-2″), 72.7 (C-3″), 49.4 (3″ OMe), 77.7 (C-4″), 66.0 (C-5″), 15.7 (2 Me), 9.6 (4 Me), 27.1 (6 Me), 23.7 (8 Me), 6.8 (10 Me), 16.2 (12 Me), 18.4 (5′ Me), 21.4 (3″ Me), 21.5 (5″ Me), 50 (α-CH_2); 27.1 (β-CH_2), 49.4 (γ-CH_2), 49.2 (α′-CH_2); 16.6 (β′-CH_2), 47.0 (α″-CH_2); 35.2 (β″-CH_2), 181.1 (NHCSNH), 119.0 (CN), 139.2 (phenyl, a), 129.0 (phenyl, b), 128.5 (phenyl, c), 126.3 (phenyl, d).

3.3.23. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-(3-phenylpropyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**10e**)

Yield 39.0%. MS *m*/*z*: (ES): $MH^+ = 1022.4$. IR (KBr) [ν/cm^{-1}]: 3438, 2970, 2935, 2870, 2248, 1726, 1530, 1455, 1377, 1167, 1053, 1012, 749, 700. ^{1}H NMR (pyridine-d_5) δ 3.18 (1H, H-2), 4.64 (1H, H-3), 2.49 (1H, H-4), 4.15 (1H, H-5), 2.00, 1.86 (2H, H-7), 2.17 (1H, H-8), 2.28; 2.71 (2H, H-9), 3.12 (1H, H-10), 4.18 (1H, H-11), 5.37 (1H, H-13), 2.17; 1.73 (2H, H-14), 0.93 (3H, H-15), 5.01 (1H, H-1′), 3.63 (1H, H-2′), 2.70 (1H, H-3′), 2.17 (6H, 3′ NMe_2), 1.69; 1.31 (2H, H-4′), 3.51 (1H, H-5′), 5.00 (1H, H-1″), 2.36; 1.59 (2H, H-2″), 3.52 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.62 (1H, H-5″), 1.36 (3H, 2 Me), 1.63 (3H, 4 Me), 1.77 (3H, 6 Me), 0.98 (1H, H-8 Me), 1.33 (3H, 10 Me), 1.39 (3H, 12 Me), 1.35 (3H, 5′ Me), 1.36 (3H, 3″ Me), 1.69 (3H, 5″ Me), 3.33 (2H, α-CH_2), 2.10 (2H, β-CH_2), 3.95; 3.75 (2H, γ-CH_2), 4.40; 4.29 (2H, α′-CH_2), 3.21 (2H, β″-CH_2), 3.98 (2H, α‴-CH_2); 2.17 (2H, β‴-CH_2), 2.70 (2H, γ‴-CH_2), 7.28 (phenyl, b), 7.23

(phenyl, c), 7.21 (phenyl, d). ^{13}C NMR (pyridine-d_5) δ 177.6 (C-1), 45.5 (C-2), 79.9 (C-3), 41.1 (C-4), 83.8 (C-5), 74.8 (C-6), 41 (C-7), 29.1 (C-8), 63.5 (C-9), 60.1 (C-10), 76.1 (C-11), 75.2 (C-12), 78.2 (C-13), 22.1 (C-14), 11.4 (C-15), 103.4 (C-1′), 71.8 (C-2′), 65.8 (C-3′), 40.5 (3′ NMe_2), 30.3 (C-4′), 68.2 (C-5′), 96.4 (C-1″), 35.7 (C-2″), 73.7 (C-3″), 49.7 (3″ OMe), 78.7 (C-4″), 66.3 (C-5″), 15.9 (2 Me), 10.4 (4 Me), 27.9 (6 Me), 23.2 (8 Me), 8.5 (10 Me), 18.4 (12 Me), 22.0 (5′ Me), 21.6 (3″ Me), 19.6 (5″ Me), 49.3 (α-CH_2); 26.4 (β-CH_2), 49.3 (γ-CH_2), 48.4 (α′-CH_2); 16.7 (β′-CH_2), 46.1 (α″-CH_2); 31.5 (β″-CH_2), 33.6 (γ″-CH_2), 182.5 (NHCSNH), 119.5 (CN), 142.5 (phenyl, a), 128.8 (phenyl, b), 128.7 (phenyl, c), 126.1 (phenyl, d).

3.3.24. 9-Deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-(1-naphthyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythromycin A (**10f**)

Yield 36.0%. MS *m*/*z*: (ES): $MH^+ = 1030.4$. IR (KBr) [ν/cm^{-1}]: 3444, 2970, 2935, 2870, 2249, 1727, 1530, 1455, 1377, 1167, 1053, 1012. ^{1}H NMR (pyridine-d_5) δ 3.18 (1H, H-2), 4.69 (1H, H-3), 2.51 (1H, H-4), 4.17(1H, H-5), 2.03 1.86 (2H, H-7), 2.24(1H, H-8), 2.77; 2.31 (2H, H-9), 3.15(1H, H-10), 4.23 (1H, H-11), 5.37 (1H, H-13), 2.16; 1.68 (2H, H-14), 0.91 (3H, H-15), 5.00 (1H, H-1′), 3.61 (1H, H-2′), 2.70 (1H, H-3′), 2.15 (6H, 3′ NMe_2), 1.39; 1.14 (2H, H-4′), 4.04 (1H, H-5′), 5.26 (1H, H-1″), 2.46; 1.56 (2H, H-2″), 3.51 (3H, 3″ OMe), 3.31 (1H, H-4″), 4.64 (1H, H-5″), 1.37 (3H, 2 Me), 1.63 (3H, 4 Me), 1.79 (3H, 6 Me), 0.98 (1H, H-8 Me), 1.34 (3H, 10 Me), 1.41 (3H, 12 Me), 1.35 (3H, 5″ Me), 1.32 (3H, 3″ Me), 1.68 (3H, 5″ Me), 3.42, 2.55 (2H, α-CH_2), 2.39 (2H, β-CH_2), 4.33, 4.08 (2H, γ-CH_2), 4.64, 4.42 (2H, α′-CH_2), 3.38 (2H, β′-CH_2), 7.72 (naphthyl, b), 7.47 (naphthyl, c), 7.79 (naphthyl, d), 7.86 (naphthyl, e), 7.43 (naphthyl, g), 7.59 (naphthyl, g), 8.49 (naphthyl, h); ^{13}C NMR (pyridine-d_5) δ 178.7 (C-1), 46.3 (C-2), 80.6 (C-3), 42.0 (C-4), 84.6 (C-5), 75.6 (C-6), 41.6 (C-7), 30.1 (C-8), 64.5 (C-9), 61.2 (C-10), 77.0 (C-11), 76.0 (C-12), 79.0 (C-13), 22.8 (C-14), 12.1 (C-15), 104.2 (C-1′), 72.6 (C-2′), 66.5 (C-3′), 41.3 (3′ NMe_2), 31.1 (C-4′), 69.0 (C-5′), 97.2 (C-1″), 36.4 (C-2″), 74.5 (C-3″), 50.5 (3″ OMe), 79.5 (C-4″), 67.1 (C-5″), 16.6 (2 Me), 11.0 (4 Me), 28.7 (6 Me), 24.0 (8 Me), 9.1 (10 Me), 19.1 (12 Me), 22.8 (5′ Me), 22.4 (3″ Me), 20.3 (5″ Me), 50.0 (α-CH_2), 27.6 (β-CH_2), 51.0 (γ-CH_2), 49.3 (α′-CH_2); 17.4 (β′-CH_2), 185.0 (NHCSNH), 120.4 (CN), 139. C(C, a, naphthyl), 128.0 (CH, b, naphthyl), 126.8 (CH, c, naphthyl), 128.3 (CH, d, naphthyl), 135.7 (C, j, naphthyl), 129.4 (CH, e, naphthyl) 127.1 (CH, f, naphthyl), 127.4 (CH, g, naphthyl), 125.4 (CH, h, naphthyl), 133.2 (C, i, naphthyl).

3.4. General procedure for the hydrolysis of **4f** and **8f**

The suspension of **4f** or **8f** (0.55 mmol) in 1 M hydrochloric acid (5 ml) was stirred for 12 h at room temperature, the pH was adjusted to 9.5–10 by adding 1 M NaOH and was extracted with CH_2Cl_2 (3 × 4 ml). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, evaporated to dryness under reduced pressure to give crude product wherefrom by chromatography on silica gel column using CH_2Cl_2:CH_3OH:NH_3 (25%) = 90:9:1.5 as eluents pure **5f** or **9f** were obtained.

3.4.1. 5-O-Desosaminyl-9-deoxo-9-dihydro-9a-[N′-(1-naphthyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythronolide A (**5f**)

Yield 88.0%. MS *m*/*z*: (ES): $MH^+ = 803.1$. ^{1}H NMR (pyridine-d_5) δ 2.99 (1H, H-2), 4.23 (1H, H-3), 2.48 (1H, H-4), 4.15 (1H, H-5), 1.87, 1.70 (2H, H-7), 2.15 (1H, H-8), 2.88; 2.24 (2H, H-9), 3.13 (1H, H-10), 4.15 (1H, H-11), 5.43 (1H, H-13), 2.24; 1.70 (2H, H-14), 0.87 (3H, H-15), 4.91 (1H, H-1′), 3.61 (1H, H-2′), 2.61 (1H, H-3′), 2.19 (6H, 3′ NMe_2), 1.37; 1.18 (2H, H-4′), 3.46 (1H, H-5′), 1.53 (3H, 2 Me), 1.49 (3H, 4 Me), 1.64 (3H, 6 Me), 1.05 (3H, 8 Me), 1.34 (3H, 10 Me), 1.38 (3H, 12 Me), 1.13 (3H, 5′ Me), 2.77 (2H, α-CH_2), 1.96 (2H, β-CH_2), 3.53 (2H, γ-CH_2), 7.57 (1H, b), 7.43 (1H, c), 8.42 (1H, d), 8.25 (1H, e), 7.34 (1H, f), 7.37 (1H, g), 7.80 (1H, h), 9.02 (1H, NH), 6.36 (1H, NH). ^{13}C NMR (pyridine-d_5) δ 177.6 (C-1), 45.7 (C-2), 78.0 (C-3), 38.6 (C-4), 93 (C-5), 74.9 (C-6), 42 (C-7), 31 (C-8), 77.7 (C-11), 75.9 (C-12), 78.2 (C-13), 22.7 (C-14), 11.6 (C-15), 105.9 (C-1′), 71.6 (C-2′), 66.2 (C-3′), 41.0 (3′ NMe_2), 30.5 (C-4′), 70.0 (C-5′), 17.2 (2 Me), 9.6 (4 Me), 28.1 (6 Me), 22.0 (8 Me), 8 (10 Me), 18.7 (12 Me), 21.8 (5′ Me), 51 (α-CH_2), 30.6 (β-CH_2), 39.4 (γ-CH_2), 157.6 (NHCONH), 136.8 (C, j), 135.3 (C, i), 129.3 (CH, h), 128.2 (CH, a), 127.0 (CH, c), 126.5 (C, g), 126.2 (CH, f), 123.9 (CH, b), 122.8 (CH, e), 119.6 (CH, d).

3.4.2. 5-O-Desosaminyl-9-deoxo-9-dihydro-9a-[N′-(β-cyanoethyl)-N′-(1-naphthyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerythronolide A (**9f**)

Yield 80.2%. MS *m*/*z*: (ES): $MH^+ = 856.1$. ^{1}H NMR ($CDCl_3$) δ 2.62 (1H, H-2), 3.31 (1H, H-3), 2.01 (1H, H-4), 3.15 (1H, H-5), 1.51, 1.33 (2H, H-7), 2.13 (1H, H-8), 2.90, 2.36 (2H, H-9), 2.97 (1H, H-10), 3.83 (1H, H-11), 4.65 (1H, H-13), 1.93; 1.57 (2H, H-14), 0.90 (3H, H-15), 3.55 (1H, H-1′), 3.09 (1H, H-2′), 2.46 (1H, H-3′), 2.36 (6H, 3′ NMe_2), 1.73; 1.13 (2H, H-4′), 3.15 (1H, H-5′), 1.16 (3H, 2 Me), 0.95 (3H, 4 Me), 1.28 (3H, 6 Me), 0.94 (1H, 8 Me), 1.14 (3H, 10 Me), 1.08 (3H, 12 Me), 1.11 (3H, 5′ Me), 3.37, 2.33 (2H, α-CH_2), 2.13, 1.73 (2H, β-CH_2), 3.87, 3.25 (2H, γ-CH_2), 3.72, 3.56 (2H, α′-CH_2), 2.79 (2H, β′-CH_2), 8.02 (1H, d, naphthyl), 7.85 (1H, e, naphthyl), 7.77 (1H, h, naphthyl), 7.58 (1H, c, naphthyl), 7.54 (1H, b, naphthyl), 7.51 (1H, f, naphthyl), 7.50 (1H, g, naphthyl). ^{13}C NMR ($CDCl_3$) δ 177.8 (C-1), 44.5 (C-2), 78.6 (C-3), 36.7 (C-4), 91.6 (C-5), 74.2 (C-6), 38.1 (C-7), 28.5 (C-8), 59 (C-9), 57 (C-10), 75.2 (C-11), 74.6 (C-12), 78.2 (C-13), 21.0 (C-14), 10.9 (C-15), 106.2 (C-1′), 70.2 (C-2′), 65.8 (C-3′), 40.3 (3′ NMe_2), 28.8 (C-4′), 69.5 (C-5′), 15.1 (2 Me), 7.8 (4 Me), 24.2 (6 Me), 22 (8 Me), 6.1 (10 Me), 16.1 (12 Me), 21.0 (5′ Me), 49.4 (α-CH_2), 27.0 (β-CH_2), 48.6 (γ-CH_2), 44.8 (α′-CH_2), 17.4 (β′-CH_2), 157.0 (NCON), 119.2 (CN), 134.9 (C, i, naphthyl), 134.4 (C, j, naphthyl), 131.4 (C, a, naphthyl), 128.1 (CH, e, naphthyl), 126.7 (CH, h, naphthyl), 126.6 (CH, c, naphthyl), 126.1 (CH, f, naphthyl), 125.9 (CH, b, naphthyl), 125.6 (CH, g, naphthyl), 123.7 (CH, d, naphthyl).

3.5. Acid stability of **4f** and **8f**

3.5.1. Preparation of **5f** hydrolysate in 0.01 M HCl

Solution of **4f** in 0.01 M HCl of concentration 1 mg/ml (100 ml) was stirred for 10 h at room temperature. After isolation and purification procedures, described in Section 3.3.1, the pure **5f** was obtained. Its ^{1}H and ^{13}C NMR spectra were identical to the spectra of the **5f** authentic sample.

3.5.2. HPLC assay and decay data

The solution of **4f** or **8f** in 0.01 M HCl aqueous hydrochloric acid (concentration of 1 mg/ml) was held at 25 °C, 30 °C, 37 °C and 40 °C for 10 h. The sample of the solution (20 μl) was taken each 20 min, and the course of reaction was monitored by the reverse phase HPLC. Each experiment was repeated three times, and displayed data represent average values.

An Agilent 1100 Series LC/MSD trap, SL model with an electrospray interface (ESI), a binary pump, degasser, autosampler, thermostatted column compartment and diode array detector was used. The analysis was carried out with UV detection at 240 nm on a YMC Pack Pro C_{18} column, 150 × 4.6 mm i.d., 3 μm particle size with a mobile phase consisted of channel A 40 mM ammonium acetate buffer solution (pH = 5) and channel B acetonitrile. Gradient elution at flow rate 1.0 ml min^{-1} started with 10% of channel B and ended after 15 min with 90% of channel B. The ESI source was operated in the positive ion mode. Nitrogen was used as nebulizing and drying gas at 350 °C. The *m*/*z* range scanned in the MS measurement was 200–1200. Complete system control, data acquisition and processing were done using the ChemStation for LC/MSD version 4.2 from Agilent.

Reaction rate constants were determined by using exponential fit method available within Excel program. The activation energies for hydrolysis of the glycosidic bond in **6a** and **6b** were calculated according to the Arrhenius equation (1).

$$\ln k = \ln A - E_a/RT \quad (1)$$

where A is the temperature factor, E_a is the activation energy, R is the ideal gas constant (8.3184 J K^{-1} mol^{-1}) and T is the thermodynamic temperature.

3.6. In vitro evaluation

In vitro susceptibility testing was performed by broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines, Document M7-A6, Vol. 20, No. 2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically; Approved Standard-Sixth Edition". Testing was performed in microdilution trays and the method was based on preparation of two-fold serial dilutions of compounds (concentrations from 64 to 0.125 μg/ml) in adequate broth (*Haemophilus* test medium – HTM – for *H. influenzae*; Mueller–Hinton broth supplemented with 5% horse serum for *Streptococci*; Mueller–Hinton broth for other bacterial species tested). Stock solutions of test compounds and standard antibiotics were dissolved in DMF (Merck) at concentration 5 mg/ml. The test organisms were prepared by adjusting turbidity of direct colony suspension of bacteria grown on fresh plates so that the final concentration of test organism after addition to the wells was approximately 5×10^4 CFU/well. Following inoculation, trays were incubated at 35 °C for 16–22 h (depending on organism). The MIC is the lowest concentration of compound that completely inhibits growth of the test organism (99% inhibition).

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