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Antibacterial Activity of Novel Sulfonylureas, Ureas and Thioureas of 15-Membered Azalides

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*Dedicated to all our colleagues engaged
worldwide in discovery and development of azithromycin,
on the occasion of the 30th anniversary of its invention (1981-2011)*

1. Introduction

One of the 20th century's significant achievements is a discovery of azithromycin (**1**) and its development to commercial product for effective treatment of various infective diseases. Owing to its exceptional therapeutic and biopharmaceutical properties, it has come to be one of the most successful antibiotics worldwide. For the discovery of azithromycin, in addition to receiving numerous awards, in the year 2000, PLIVA's scientists Slobodan Djokic and Gabrijele Kobrehel together with the representatives from the US-based Pfizer, Gene Michael Bright and Arthur E. Girard, (Anonymous, 2000) were granted the honourable titles of "Heroes of Chemistry" by the American Chemical Society (ACS), a non-profit association of American chemists and chemical engineers, and the largest association of scientists in the world. This prestigious award is taken to be also recognition of the achievement of PLIVA's entire team working on azithromycin. The success of azithromycin has positioned PLIVA among the few pharmaceutical companies in the world that have developed their own blockbuster drug, and has entitled Croatia to join a small group of nations that have developed a new antibiotic.

Nowadays, on the occasion of the 30th anniversary of azithromycin's invention (1981-2011) an increasing prevalence of antibiotic-resistant pathogens suggests that we deeply entered into a "Post-Antimicrobial Era" (Cohen 1992; Travis 1994; Kirst 1996b). Investment in newer anti-infective platforms is essential and urgent in order to achieve a significant progress in our understanding of bacterial resistance and new approaches how to control it.

Macrolides as polyketide class of natural products have a long history as effective therapeutic agents for treating infectious diseases (Schönfeld & Kirst, 2002; G.T. Hansen et al., 2002; T. Kaneko et al., 2006). The popularity of this class of antibiotics, inhibiting bacterial protein synthesis by interfering with ribosome function, is largely due to their spectrum of activity and their relative safety. They are still in the centre of interest of many research groups from academic institutions 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 (Sunazuka et al. 2002; Pal 2006). Antibacterial macrolides have attracted considerable attention for two main reasons: (a) the emergence of atypical and/or new pathogens and extensive clinical application of these antibiotics had resulted in an increasing emergence of bacterial resistance, especially among macrolide-resistant *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus* strains, and, therefore, the development of alternative antibacterial agents became essential; (b) macrolide derivatives, especially 14- and 15-membered classes, have also become interesting for treating important chronic diseases, that is, asthma, chronic sinusitis, diffuse panbronchiolitis, cystic fibrosis (Čulić, 2001; Labro, 2000; Labro, 2004), bronchiolitis obliterans syndrome (BOS) (Vanaudenaerde et al., 2008; Culic et al., 2006), etc. Some macrolides proved active in treatment of malaria (Andersen et al., 1994; Kuschner et al., 1994; Andersen et al., 1995; Ohrt et al., 2002; Sidhu et al., 2007) and cancer (Romano et al., 2004; Oyelere et al. 2009; Mwakwari et al. 2010; Bao et al., 2010), showed antiparasitic activity (Lee et al. 2011) or act as motilides, *ie.* macrolides with gastrointestinal motor stimulating activity (Takanashi et al. 2009).

Following this trend, the chemists from PLIVA Pharmaceuticals (Zagreb, Croatia) discovered in 1980 the famous azithromycin molecule, 1 (Fig. 1), characterized by unique 15-membered macrolide ring system, having a basic methylamino group inserted into the erythromycin aglycone (Kobrehel & Djokić 1982; Kobrehel et al., 1982; Kobrehel & Djokić, 1985; Djokić et al. 1986; Djokić et al. 1987; Djokić et al. 1988). Soon after the publication of PLIVA's Belgian azithromycin patent, researchers at Pfizer (Groton, USA) prepared azithromycin independently, as the results of their own research program (Bright 1984).

Azithromycin was, beside clarithromycin, the leader of the second-generation of macrolides, the first representative of new series of macrolides termed "azalides" (Schönfeld & Mutak 2002; Mutak 2007), and today the golden standard for macrolide antibiotics (Spaventi 2002).

Azithromycin has broad spectrum of activity against all relevant bacteria causing respiratory tract infections, including *Haemophilus influenzae* and *Moraxella catarrhalis* (Mutak, 2007). It also possesses excellent safety and tolerability profiles and is widely prescribed for the treatment of upper and lower respiratory tract infections (Kirst, 1996a; Girard et al., 1987; Schönwald et al, 1991; Retsema et al., 1986). The greatest advantages of azithromycin compared to other macrolide antibiotics are its unusual pharmacokinetics: high tissue distribution and metabolic stability. These properties have led in recent years to the widespread use of the azalide scaffold for synthesis of new antibacterial active compounds with advantageous pharmacokinetics.

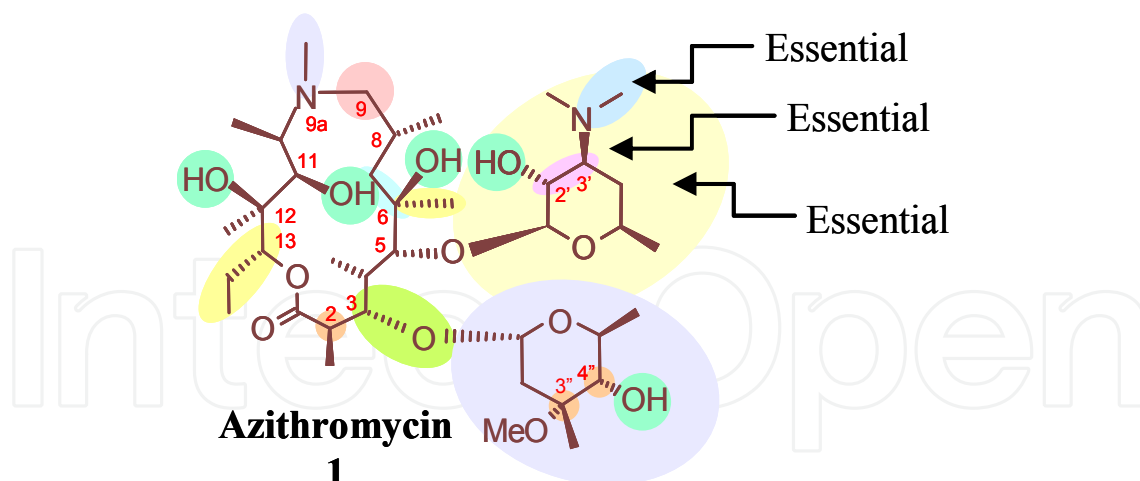


Fig. 1. Azithromycin (**1**) and its position subjected to derivatization

The growing resistance to antibiotics conferred by microorganisms commonly involved in respiratory tract infections has become a serious clinical problem (Prieto et al., 2002). The widespread use of macrolides has contributed to the increase of resistance within *Streptococcus pyogenes* and *Streptococcus pneumoniae* strains and its level varies worldwide, with an alarming upper rate of 25% in some European countries (Granizo et al., 2000; Szczypa et al., 2000; Nagai 2002 et al.,; Albrich et al., 2004). Gram-positive *S. pyogenes* and *S. pneumoniae* is the most common bacterial strains implicated in acute pharyngitis, skin and soft tissue infections and also one of the most problematic respiratory pathogen (Cunningham et al., 2000).

It has been shown that the resistance to macrolide antibiotics in Gram-positive microorganisms can be attributed to two main mechanisms: target site modification and active efflux (Nakajima et al., 1999). It is known that macrolides exert their activity by binding to the large 50S ribosomal subunit. They inhibit bacteria protein synthesis at peptidyl transferase center by blocking the nascent peptide exit tunnel (Poehlgarrd & Douthwaite 2003). The modification of specific rRNA bases can prevent macrolides to bind. This may be due to the action of methylases encoded either by *erm(B)* or *erm(A)* genes (Weisblum, 1998). The methylases are responsible for developing macrolide, lincosamide and streptogramin B (MLS_B) resistance; inducible-(iMLS) or constitutive (cMLS). The active drug efflux is another common type of resistance developed by bacteria and is mediated by the membrane-associated pump encoded by the *mef(A)* gene (Sutcliffe et al. 1996). In order to overcome the resistance problems, lots of efforts have been made worldwide to search for novel and more potent agents with all of the desirable features of the earlier generation of macrolides.

The discovery of highly potent representatives of the third-generation of macrolides, like ketolides (Agouridas 1998), acylides (Tanikawa et al. 2001; Tanikawa et al. 2003), anhydrolides (Elliott et al. 1998), etc., was a step forward to tackle the efflux problems (LeMahieu et al. 1974; Pestka & LeMahieu 1974a & 1974b, Pestka et al. 1974; Pestka et al. 1976; Allen. 1977; Van Bambeke et al. 2008) to (Tanikawa et al., 2001; Tanikawa et al., 2003), anhydrolides (Elliott et al., 1998), etc., was a step forward to tackle the efflux problems (LeMahieu et al., 1974; Pestka & LeMahieu 1974a & 1974b, Pestka et al., 1974; Pestka et al., 1976; Allen. 1977; Van Bambeke et al., 2008).

However, some serious drawbacks have been observed for those compound classes: the emergence of resistance developed shortly after their introduction and rare but serious side effects which lead to restrictions and withdrawal (Bambeke et al., 2008) as seen recently with telithromycin, approved by the United States (USA) Food and Drug Administration (FDA) approved in 2004 by for treatment of mild to moderate community-acquired bacterial pneumonia (CABP) (Cruzan, 2007; Farrell et al., 2010).

Recently, considering azithromycin's beneficial pharmacokinetic properties, our group have led the widespread modification of the azalide scaffold (Fig. 1) in a search for new, to resistant bacterial strains active azalides (Fajdetic et al., 2010; Fajdetic et al., 2011; Hutinec et al., 2010; Kapić et. al, 2010; Kapić et. al, 2011a; Kapić et. al., 2011b; Marušić Ištuk et al., 2011; Matanović Škugor et al., 2010; Palej Jakopović et al., 2010; Pavlović et al., 2010; Pavlović & Mutak, 2011; Štimac et al., 2010).

In this paper, we present the short overview leading to the discovery of novel sulfonylureas, ureas and thioureas of 15-membered azalides as a new class of compounds and their antibacterial activity against some key erythromycin resistant pathogens. Structural features that guided design of novel macrolides included (1) a properly attached aryl/heteroaryl-carbamoyl group for improving activity against MLS_B resistance and (2) cleavage of cladinose sugar and ketolide backbone for improving potency and activity against efflux resistance. It was expected that introduction of unsaturated unit, that is, carbamoyl group, on nitrogen at position 9a of **1** (Fig. 1) will significantly change electronic properties and also steric environment in the 'upper part' of the macrolide. It will also serve as an excellent linker for the attachment of various groups affording preparation of a library of compounds with the goal of identifying novel bacterial inhibitors.

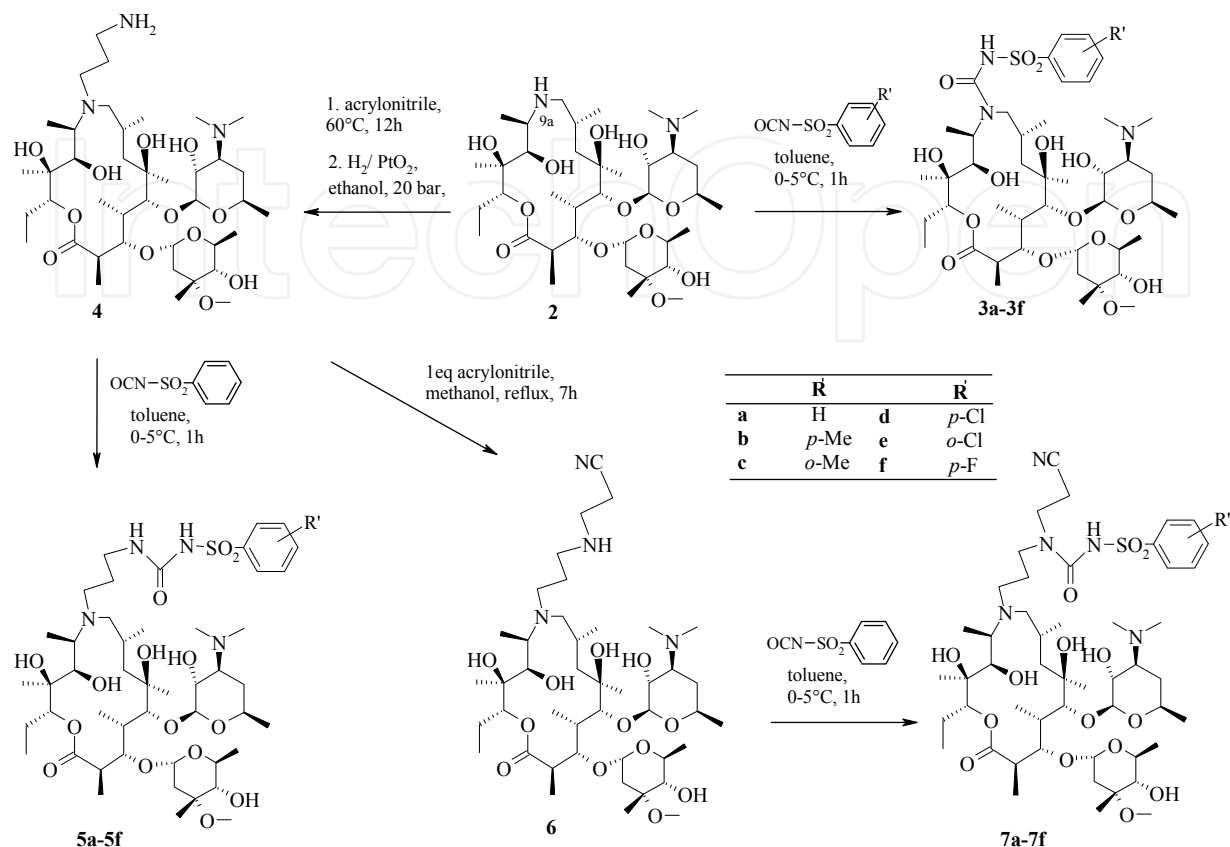
2. Novel sulfonylureas, ureas and thioureas of 15-membered azalides

The first discovered representative of the 15-membered azalides, cyclic amine **2** (Scheme 1) named 9-deoxo-9a-aza-9a-homoerythromycin A, permitted a derivatisation line at the 9a-nitrogen atom (Scheme 1). Its first derivatization was methylation at 9a position and synthesis of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, azithromycin (**1**) (Kobrehel & Djokić, 1982).

Several *N*-derivatisation lines of azalides skeleton were started in PLIVA in the early 1990s (Schönfeld & Mutak 2002; Mutak 2007), and some of the synthesized compounds showed antibacterial activity. In that respect, the observed activity of initially prepared 9a-*N*-carbamoyl and *N*-thiocarbamoyl derivatives of **2** (Kujundžić et al., 1995) encouraged us to extend our study in this direction.

Thus, a series of new sulfonylurea, urea and thiourea derivatives of 15-membered azalides were prepared in order to study whether antibacterial activity toward resistant strains would be achieved by introduction of aryl-sulfonylcarbamoyl/carbamoyl/thiocarbamoyl group into the azalide molecule and how the activity would be affected by nature and position of the substituents in the phenyl ring (Bukvić Krajačić et al., 2005). Of particular interest was to study the influence of the linker between sulfonylcarbamoyl/carbamoyl/thiocarbamoyl- group and

aglycon moiety on the antibacterial activity. A special attention was paid to achieving the activity against *S. pyogenes* and *S. pneumonia* resistant strains.



Scheme 1. Synthesis of sulfonylureas **3**, **5** and **7**.

2.1 Sulfonylureas

Intermediates **2** (Djokić et al., 1986; Djokić et al., 1988) and **4**, smoothly reacted with substituted benzenesulfonyl isocyanates to form 9a-*N*-[*N'*-(aryl)sulfonylcarbamoyl] derivatives, **3a-3f** and **5a-5f** in high yields (Scheme 1). The key intermediate, 9a-*N*-(γ -aminopropyl) derivative **4** was prepared by standard Michael addition of acrylonitrile to the amine **2**, followed by catalytic hydrogenation of obtained 9a-*N*-(β -cyanoethyl) derivative with PtO₂ as a catalyst (Bright et al., 1988). Derivatives **7a-7f**, were prepared by the selective cyanoethylation of amine **4** with equivalent amounts of acrylonitrile, followed by the addition of the substituted benzenesulfonyl isocyanates to the intermediate **6**.

For the sulfonylureas directly linked to macrocyclic ring **3a-3f** it was observed that compounds with methyl group and chlorine in *p*- **3b** (MIC 1 μ g/ml), **3d** (MIC 1 μ g/ml) and *o*- **3c** (MIC 0.5 μ g/ml), **3e** (MIC 2 μ g/ml) positions and fluorine in *p*-position **3f** (MIC 2 μ g/ml) showed significantly improved activity against iMLS resistant *S. pyogenes* strain when compared to azithromycin **1** (MIC 8 μ g/ml) and starting amine **2** (MIC 16 μ g/ml). Also, these compounds exhibited two level of dilution better activity than **2** (MIC 0.25 μ g/ml) and similar activity to **1** (MIC \leq 0,125 μ g/ml) against sensitive *S. pneumonia* (Bukvić Krajačić et al. 2005). However, the activities against Gram-negative bacteria were all lower than those for **1** and **2**. Generally, it was observed that antibacterial activity of the novel

arylsulfonylcarbamoyl derivatives **3a-3f**, **5a-5f** and **7a-7f** against all the tested erythromycin susceptible (Ery-S) Gram-positive strains decreased in the series **3a-3f** > **5a-5f** > **7a-7f** by the introduction of a propyl linker and additional cyanoethyl side chain.

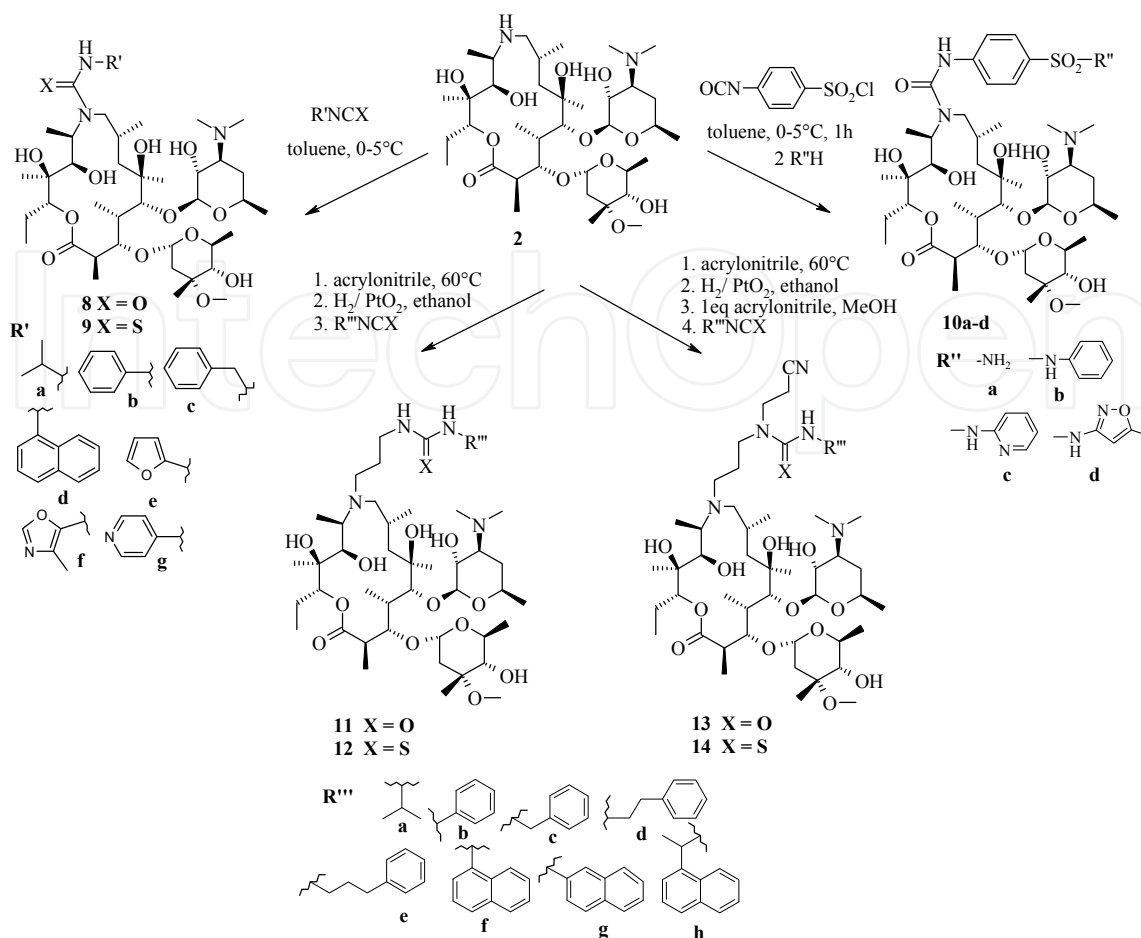
2.2 Novel ureas and thioureas & macrolide-sulfonamide conjugate

Various 9a-carbamoyl and thiocarbamoyl derivatives **8** & **9** were prepared (Scheme 2) by reaction of intermediate **2** with corresponding isocyanates or isothiocyanates (Kujundžić et al., 1995). Reactions were usually conducted in toluene to achieve easily crystallisable *N*-alkyl or *N*-aryl substituted ureas. Structures of the *N*-isopropyl- (**8a**) (Kujundžić et al., 1995) and *N*-(4-pyridyl)- (**8g**) (Sheldrick et al., 1995) derivatives were confirmed by single crystal X-ray analysis. In biological testing, only a few derivatives **8** & **9** showed moderate antibacterial activity. Additional halogen-aryl derivatives of **8** & **9** have been synthesized showing moderate activity against resistant strains (Marušić-Ištuk et al., 2000).

Introduction of novel interactive groups into the azalide backbone resulted in further improvements in activity. Strategy which involved macrolide conjugates incorporating antibacterial sulfonamides, such as sulfanilamide, sulfabenz, sulfapyridine and sulfamethoxazole, showed an increased affinity for the ribosome (Bukvić Krajačić et al., 2007). Significant activity against inducible resistant *S. pyogenes* strains was observed by modifications at position 9a of an azalide lacton ring, by the carbamoyl group linked sulfonamides (Scheme 3). Conjugates of 15-membered azalides and sulfonamides **10a-10d** were prepared by the reaction of **2** (Djokić et al. 1986; Djokić et al. 1988) with 4-(chlorosulfonyl)phenylisocyanate. The smoothly formed 9a-(4-chlorosulfonylphenyl)-carbamoyl derivative was transformed without the isolation into the compounds **10a-10d**, by the reaction of ammonia, aniline, 2-aminopyridine and 5-methyl-3-aminoisoxazole, respectively.

Azalide-sulfonamide conjugates **10a** and **10b** possess two to three times better activity against iMLS resistant *S. pyogenes* strain (MIC 2 µg/ml) when compared to both azithromycin **1** (MIC 8 µg/ml) and starting cyclic amine **2** (MIC 16 µg/ml) (Bukvić Krajačić et al., 2007). These activities are comparable to those observed for azalide sulfonylureas **3a-3f** (Bukvić Krajačić et al., 2005). New azithromycin-sulfonamide conjugates **10a** and **10b** exhibit somewhat lower activity than **1** against sensitive *S. pneumonia* and *S. pyogenes* strains. Furthermore, the **10c** and **10d** showed in general lower activity against most of the tested bacterial strains except for sensitive *S. aureus* and *M. catarrhalis* where better activity was observed in comparison with **10a** and **10b** analogs (Bukvić Krajačić et al., 2007).

Further expanding the range of antimicrobial activity, especially against MLS_B and efflux-mediated resistant *S. pyogenes* and *S. pneumoniae* strains was achieved by introduction of carbamoyl and thiocarbamoyl groups attached on propyl linker at the 9a position (Bukvić Krajačić et al., 2009). Novel *N'*-aryl substituted 9a-(*N'*-carbamoyl/thiocarbamoyl-γ-aminopropyl)- **11**, **12** and 9a-[*N'*-(β-cyanoethyl)-*N'*-(carbamoyl/thiocarbamoyl-γ-aminopropyl)]- **13**, **14** derivatives were obtained according to efficient procedure described for the preparation of the previous classes of compounds (Scheme 2) (Bukvić Krajačić et al., 2005 & 2007).



Scheme 2. Synthesis of novel ureas and thioureas of 15-membered azalides and azalide-sulfonamide conjugates

Ureas **11** and **13** and thioureas **12** and **14** (Bukvić Krajačić et al., 2009) showed a significant improvement in antibacterial activity against all tested macrolide-susceptible and resistant bacteria in comparison with carbamoyl/thiocarbamoyl derivatives **8** & **9** (Kujundžić et al. 1995), sulfonylcarbamoyl derivatives **3a-3f** (Bukvić Krajačić et al., 2005) and azithromycin-sulfonamide conjugates **10a-10d** (Bukvić Krajačić et al., 2007). Also, these compounds exhibited a substantially improved *in vitro* antimalarial activity against *P. falciparum* (Bukvić Krajačić et al., 2011b; Hutinec et al., 2011). Several ureas bearing naphthyl substituents (**11f**, **11g**, **11h**) were superior *in vitro* to the azithromycin against inducible resistant *S. pyogenes* (MIC 2 $\mu\text{g/ml}$). Ureas **11f**, **11g** and thioureas **12c**, **12d**, **12e**, **12f** possess good activity against efflux-mediated resistant *S. pyogenes* (MIC 4 $\mu\text{g/ml}$), comparable to azithromycin (MIC 4 $\mu\text{g/ml}$).

In general, all tested compounds had high *in vitro* activity against erythromycin susceptible Gram-positive aerobes, *S. pneumoniae* and *S. pyogenes* (MIC ≤ 0.125 $\mu\text{g/ml}$) (Bukvić Krajačić et al., 2009). Ureas **11** and **13** and thioureas **12** and **14** exhibited excellent activity against susceptible *S. aureus* (MIC 0.25-1 $\mu\text{g/ml}$), but lacked activity against resistant *S. aureus* strains. Ureas **11f**, **11g** and thiourea **12f** also showed *in vitro* activity against efflux-mediated resistant *S. pneumoniae* with MICs 4 $\mu\text{g/ml}$ and their activities were comparable with those observed for azithromycin (MIC 8 $\mu\text{g/ml}$). Ureas **11g**, **11h** and **13h** showed moderate activity against cMLS *S. pneumoniae* (MIC 16 $\mu\text{g/ml}$) (Bukvić Krajačić et al., 2009). *In vitro* activities of ureas **11** and **13**, thioureas **12** and **14** against key community-acquired Gram-negative respiratory pathogens

were improved in comparison with sulfonyleureas **3a-3f** (Bukvić Krajačić et al., 2005) and azithromycin-sulfonamide conjugates **10a-10d** (Bukvić Krajačić et al., 2007). Ureas **11f**, **11g** and **11h** demonstrated high activity against *Moraxella catarrhalis*. Naphthyl substituted ureas **11f**, **11g** and **11h** showed better activity against Gram-negative pathogens involved in respiratory tract infections (RTI), *M. catarrhalis* (MIC 0.25 µg/ml) and *H. influenza* (MIC 1 µg/ml) than derivatives with phenyl ring on the alkyl side-chain **11b-11d**. In case of phenylethyl-substituents in **11d** and **12d** the presence of thiocarbamoyl moiety seemed to improve activity against *H. influenzae*. The urea **13** with cyanoethyl chain showed similar antibacterial activity in comparison to the urea **11**. The observed antibacterial activity of ureas and thioureas increased in the series **8 & 9 < 11 & 12 < 13 & 14**, by the introduction of a propyl linker and additional cyanoethyl side-chain (Bukvić Krajačić et al., 2009).

On the basis of excellent *in vitro* antibacterial activity and their structural similarity, several compounds **11f**, **11g**, **11h**, **12c**, **12d**, **12e**, **12f**, **13h**, **14c**, **14d**, **14e** were screened for acid stability, cytotoxicity and preliminary pharmacokinetic parameters. In acidic conditions compounds exhibited azithromycin like stability (Bukvić Krajačić et al., 2009). *In vitro* cytotoxicity on Hep G2 and THP-1 cell lines measured for the selected set of compounds revealed that all compounds showed relatively low cytotoxicity *in vitro* (IC₅₀s ≥ 4 µM) (Bukvić Krajačić et al., 2011b). These marked them as potent and selective compounds for further profiling (Steinmeyer, 2006). Metabolic stability of ureas and thioureas were screened *in vitro* using human and mouse liver microsomes and only a few were selected for *in vivo* rat pharmacokinetic studies in order to determine their pharmacokinetic profiles (Table 1) (Bukvić Krajačić et al., 2011b). All compounds demonstrated good *in vitro*, metabolic stability with t_{1/2} greater than 120 min (t_{1/2} = 103 min for compound **14d** in human liver microsomes). As was observed with azithromycin, and in line with the *in vitro* data, these analogs had a low systemic clearance, moderate to high volume of distribution and a very long half-life, however, the oral bioavailability was low (**12c**, **12e**) to moderate (Bukvić Krajačić et al., 2011b).

	CL (mL/min/kg)	Vd (L/kg)	t _{1/2} (hr)	Oral F (%)
Azithromycin	11.0	20.0	24.0	33.0
12c	4.0	10.4	30.0	3.4
12e ^a	2.3	2.6	13.4	1.3
14e	24.5	31.7	15.2	21

CL - blood clearance, Vd - apparent volume of distribution at the terminal phase based on drug concentration in blood, t_{1/2} - half life, ^a - IV parameters determined in one rat

Table 1. Pharmacokinetic parameters estimated in blood after intravenous (IV) and oral gavage (PO) administration to Sprague-Dawley rats (10 mg/kg IV and 30 mg/kg PO) (Bukvić Krajačić et al., 2011b).

Preliminary *in vitro* microsomal stability data indicated that these compounds had good metabolic stability, as was confirmed by low clearances *in vivo* for the compounds tested. In comparison to azithromycin, known for its extensive tissue distribution, (Schönfeld & Mutak, 2002) these derivatives had a tendency toward higher volumes of distribution, in line with their increased lipophilic character (approx. 2-3 log units higher than azithromycin, according to calculated logP values, data not shown) due to the presence of strong lipophilic aromatic phenyl and naphthyl rings in the 9a-N substituent (Bukvić Krajačić et al., 2011b). Overall, with increased *in vitro* activity and promising *pharmacokinetic* properties, this series of molecules represents a good starting platform for the design of novel antibacterial and antimalarial azalides.

2.3 3-Decladinosyl-derivatives of sulfonylureas, ureas and thioureas

Introduction of unsaturated, sp^2 hybridized, carbamoyl unit at 9a position placed nitrogen atom of **2** significantly change electronic properties and also steric environment in the 'upper part' of the macrolide, what resulted in increased antibacterial activity of the novel sulfonylureas **3,5,7** (Bukvić Krajačić et al., 2005), azalide-sulfonamide conjugates **10** (Bukvić Krajačić et al., 2007), and ureas and thioureas **11-14** (Bukvić Krajačić et al., 2009). On the other hand, the selectively achieved cleavage of cladinose sugar, significantly changes the structural behaviour of the 'lower part' of 9a-carbamoyl 15-membered azalides, leading to the 3-*O*-decladinosyl-3-hydroxy ureas and thioureas lacking of any, as expected, antibacterial activity (Bukvić Krajačić et al., 2005; Bukvić Krajačić et al., 2007; Marušić Ištuk et al., 2007).

However, there are some novel highly potent 3-*O*-decladinosyl derivatives of 14-membered macrolides, e.g. ketolides (Agouridas et al, 1998), acylides (Tanikawa et al., 2001; Tanikawa et al., 2003), anhydrolides (Elliott et al., 1998), etc. (Schönfeld & Kirst 2002; Pal 2006; Kaneko et al. , 2006; Mutak 2007) (Fig. 2), proved active against resistant bacterial strains.

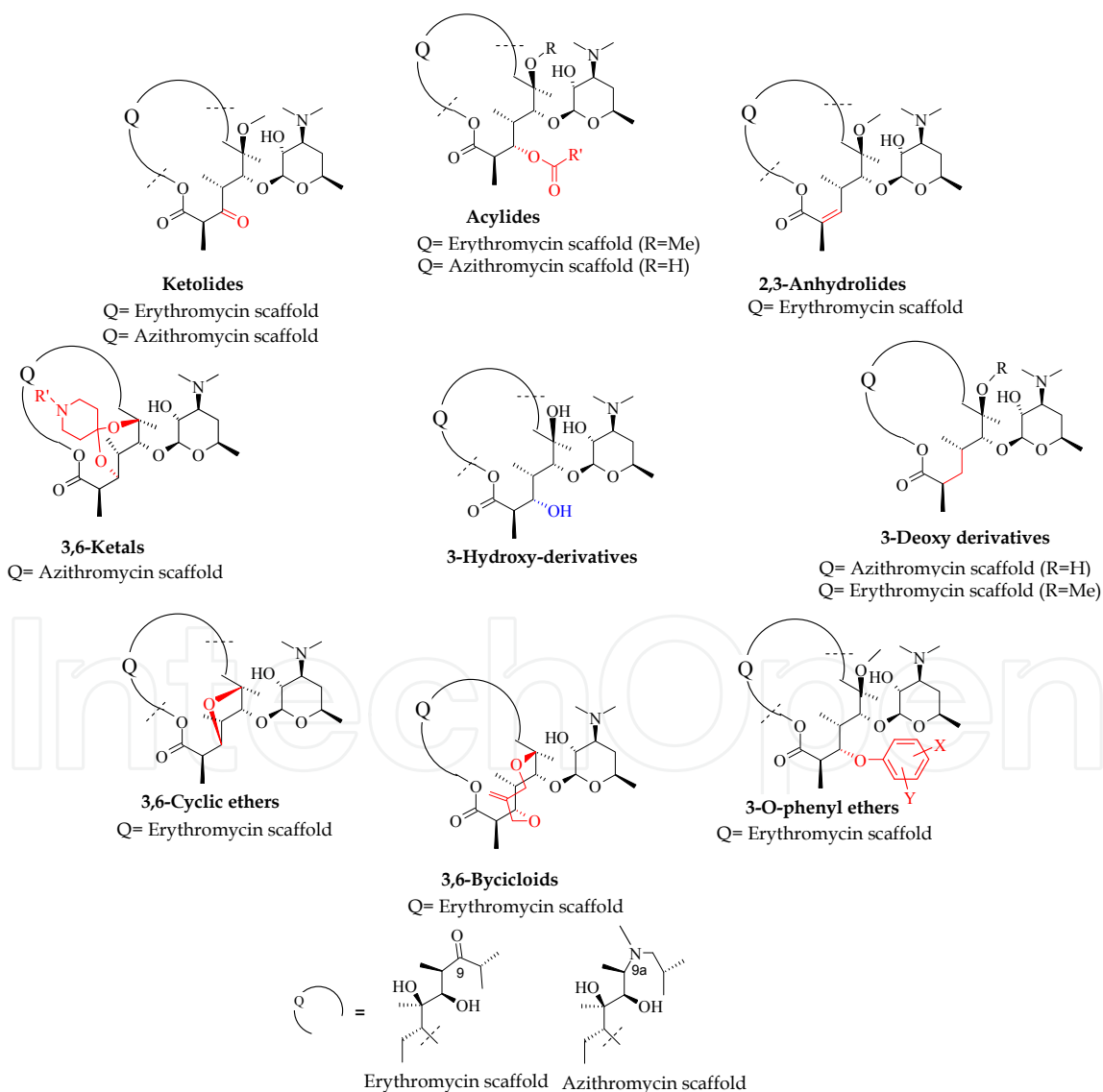
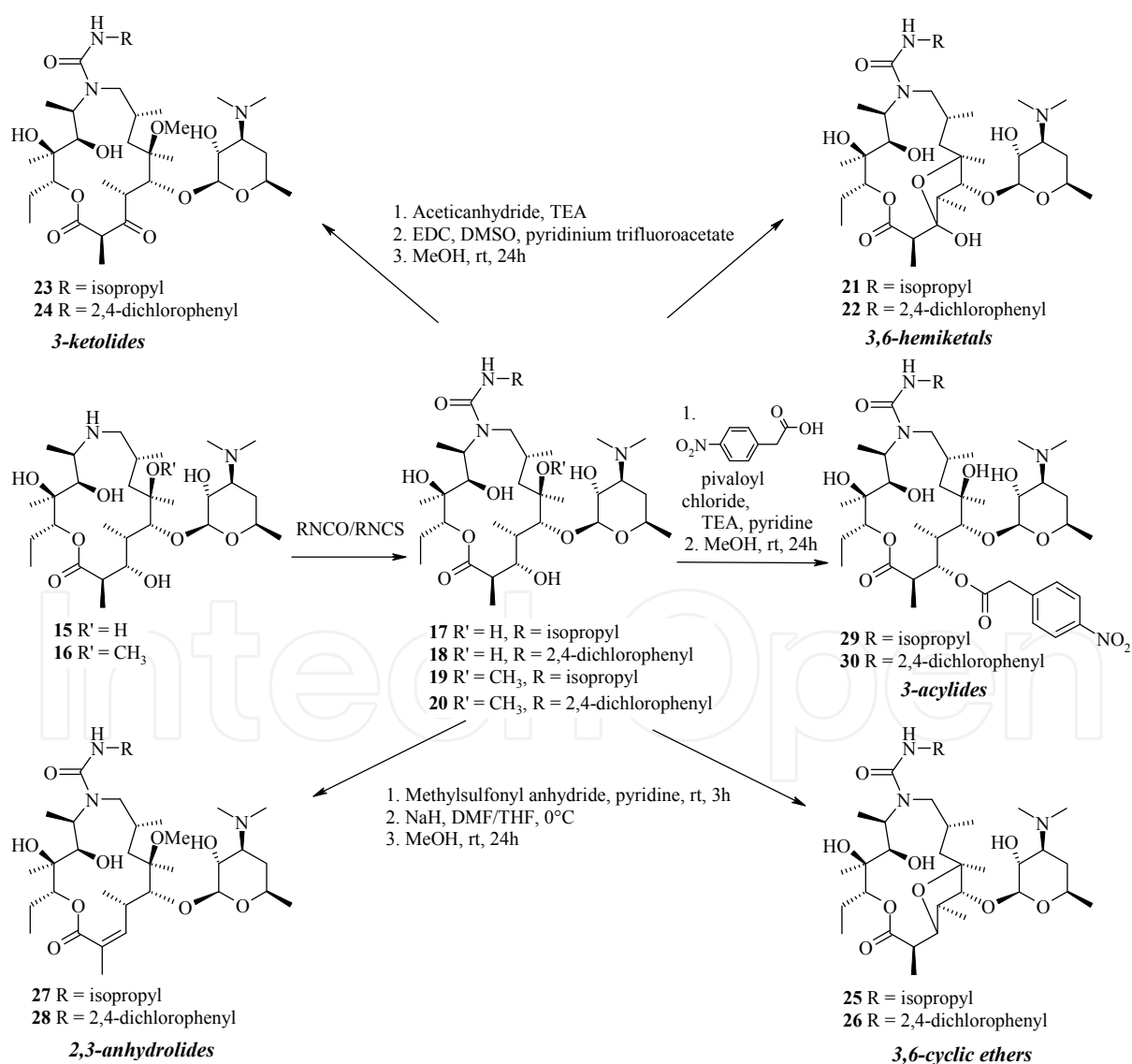


Fig. 2. Novel classes of 3-*O*-decladinosyl derivatives of 14- and 15-membered macrolides

2.3.1 3-Decladinosyl-3-O-substituted derivatives

Isopropyl- and 2,4-dichlorophenyl- derivatives of 9a-carbamoyl-6-hydroxy (**17** & **18**) and 9a-carbamoyl-6-methoxy azalides (**19** & **20**) lacking any antibacterial activity, were selected to study the effects of the 'lower part' of azalide skeleton modifications *via* chemical transformations of hydroxyl group at C-3 position (Scheme 3) (Marušić Ištuk et al., 2007). They afforded formation of the new ketolides **23** and **24**, anhydrolides **27** and **28**, hemiketals **21** and **22**, cyclic ethers **25** and **26**, and acylides **29** and **30** (Scheme 4). In order to perform chemical transformations on the hydroxyl group at position 3, 2'-hydroxyl group which is the most reactive one, was suitably protected. Consequently, reaction of 3-decladinosyl-3-hydroxy- azalides **17**, **18**, **19**, and **20** with acetic anhydride in the presence of a base smoothly afforded 2'-O-acetyl-3-decladinosyl-3-hydroxy-6-hydroxy azalides, that under conditions of Pfitzner-Moffat 3-OH group oxidation, followed by subsequent methanolysis of 2'-O-acetyl intermediate produces internal 3,6-hemiketal structures **21** and **22**. Under the same reaction conditions 2'-O-acetyl-3-decladinosyl-3-hydroxy-6-methoxy derivatives afford 3-keto azalides **23** and **24** (Scheme 3). Introduction of mesyl group at position C-3 of 6-hydroxy-, **17**



Scheme 3. Synthesis of 3-decladinosyl-3-O-substituted azalides

& **18**, and 6-methoxy-, **19** & **20** derivatives and subsequent base-promoted elimination led to the formation of different products. Whereas 6-hydroxy derivatives **17** & **18** produce 3,6-cyclic ethers **25** and **26**, 6-methoxy derivatives **19** & **20** afford 2,3-anhydro azalides **27** and **28**.

Among already known 3-acylides of 14-membered macrolides, 3-*O*-(4-nitrophenyl)acetyl derivative of clarithromycin (TEA-0777) showed the best antibacterial activity (Tanikawa et al., 2001). Accordingly, 9a-carbamoyl acylides having (4-nitrophenyl)acetyl- functionality attached to 3-*O* position, azalides **29** and **30**, were prepared, to test if antibacterial activity could be enhanced upon attachment of favorite side-arm.

3-Decladinosyl-6-hydroxy and 6-methoxy azalides **15** and **16** and 9a-carbamoyl/9a-thiocarbamoyl derivatives **17**, **18**, **19** & **20** proved antibacterially inactive against tested strains. Similar situation can be seen with 3,6-hemiketals **21** & **22** and 3,6-cyclic ethers **25** & **26**. However, anhydrolides **27** and **28** as well as ketolides **23** and **24** show good antibacterial activity against efflux resistant *S. pneumonia* but lower in comparison to erythromycin. 9a-Carbamoyl-3-*O*-(4-nitrophenyl)acetyl- acylides **29** and **30** showed the best antibacterial activity against efflux resistant *S. pneumoniae* (MIC 4 µg/ml), and better in comparison to erythromycin (MIC 8 µg/ml). Acylides **29** and **30** also show weak activity against erythromycin-resistant *S. aureus* (Marušić Ištuk et al., 2007).

2.3.2 3-Decladinosyl-3-hydroxy derivatives

As expected, 3-decladinosyl-3-hydroxy- azalides **17** – **20** and **31** - **34** (Fig. 3) lacked any significant antimicrobial activity (Marušić Ištuk et al., 2007; Bukvić Krajačić et al., 2005; Bukvić Krajačić et al., 2007) being consistent with the role cladinose was found to play in antimicrobial activity (LeMahieu et.al., 1974; Kaneko et.al., 2006; Pal, 2006; Tanikawa et.al., 2001; Mutak, 2007).

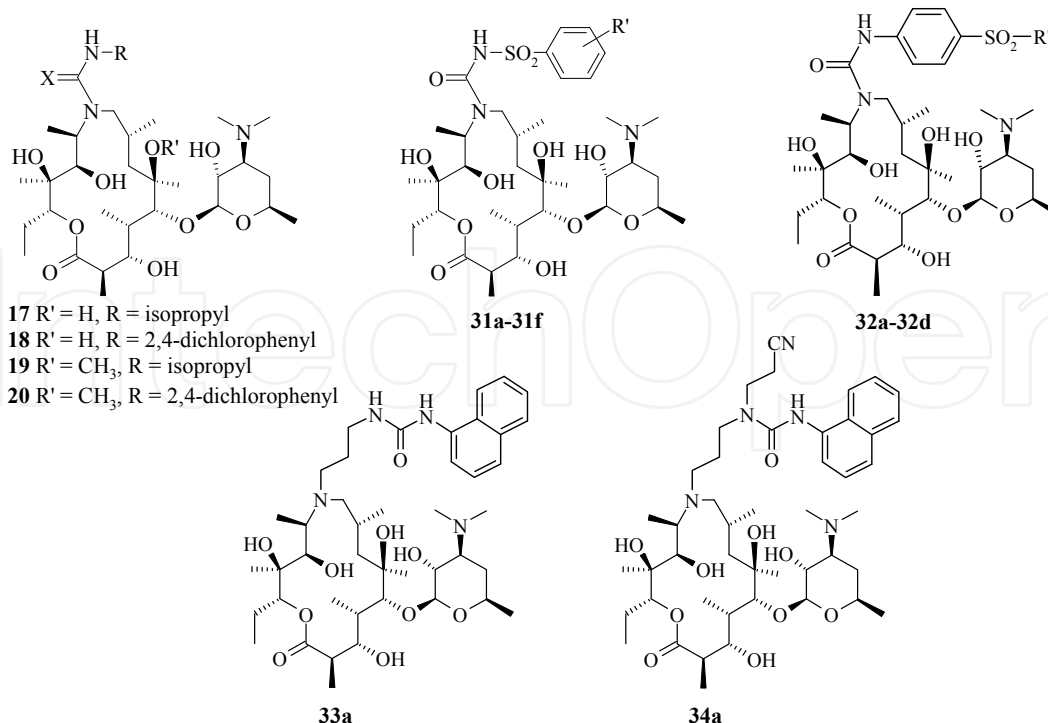
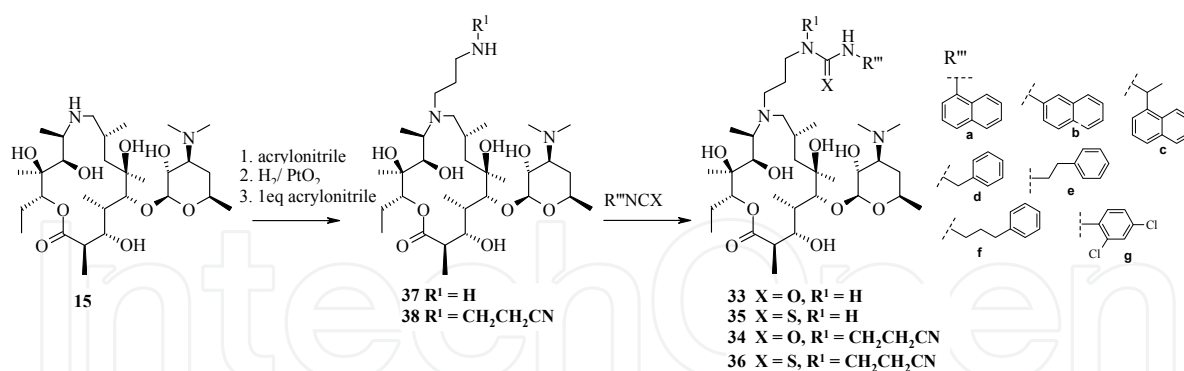


Fig. 3. 3-Decladinosyl-3-hydroxy- azalides from the urea, thiourea and sulfonylurea series, lacking any significant antimicrobial activity

This is supported by recently published NMR binding studies (trNOESY and STD experiments) on 6-*O*-methyl-homoerythromycin derivatives, showing that the absence of cladinose sugar has been found to be the main cause of their inability to bind to their target ribosome (Novak et al., 2009). Stability study of the most active compounds **11f** and **13f** in the artificial gastric juice (Bukvić Krajačić et al., 2009) led to the formation of two decladinosyl derivatives **33a** and **34a** which were tested only against panel of *S. pneumoniae* strains. As was expected decladinosyl urea derivative **34a** did not show activity against tested strains. However, decladinosyl urea derivative **33a** showed significant activity against erythromycin susceptible *S. pneumoniae* strain (1 µg/ml), as well as efflux-mediated *S. pneumoniae* resistant strain (8 µg/ml) comparable to azithromycin. This finding initiated the synthesis of a small library of 3-decladinosyl-3-hydroxy ureas and thioureas of 15-membered azalides termed “decladinosylides” (Bukvić Krajačić et al., 2011a).

High reactivity of secondary and primary amino groups of 3-decladinosyl- derivatives **37** and **38** toward isocyanates and isothiocyanates assured highly site-selective introduction of carbamoyl and thiocarbamoyl groups and preparation of ureas **33** & **34** and thioureas **35** & **36** in high yield (Scheme 4). They were found to possess good antibacterial activities against key respiratory Gram-positive and Gram-negative pathogens including efflux-mediated resistant strains.

Among them, most of the synthesized 3-decladinosyl-3-hydroxy derivatives showed moderate to high activity against efflux-mediated resistant *S. pneumoniae* and moderate activity against susceptible *S. pneumoniae* and *S. pyogenes* strains. Against efflux-mediated resistant *S. pneumoniae* compound **35a** (MIC 2 µg/ml) possesses better activity compared to azithromycin (**1**) (MIC 8 µg/ml) (Bukvić Krajačić et al., 2011a) and their parent 3-cladinosyl analogues **11** & **13** (MIC 4 to 16 µg/ml) (Bukvić Krajačić et al., 2009), and significantly better in comparison to the 3-decladinosyl-3-hydroxy azithromycin (**16**) (MIC >64 µg/ml).



Scheme 4. Synthesis of novel 3-decladinosyl ureas and thioureas of 15-membered azalides.

The racemic urea derivative **33c** showed the highest activity against both, susceptible *S. pneumoniae* and *S. pyogenes* strains, and the same activity as its 3-cladinosyl analogue (\pm)-**11h** and azithromycin (MIC \leq 0.125 µg/ml) (Bukvić Krajačić et al., 2009).

Interestingly, some of discovered 3-decladinosyl-3-hydroxy ureas **33** & **34**, and thioureas **35** & **36**, maintain antibacterial activity against Gram-negative pathogens *H. influenzae* and *M. catarrhalis* (Bukvić Krajačić et al., 2011a) in comparison to their parent 3-cladinosyl derivatives **11**, **12**, **13** & **14**, (Bukvić Krajačić et al., 2009) and demonstrate large improvement in comparison to the inactive 3-decladinosyl sulfonylureas **31** (Bukvić Krajačić et al., 2005)

and 3-decladinosyl azithromycin-sulfonamide conjugates **32** (Bukvić Krajačić et al., 2007). Activity of (\pm)-**33a** and **35a** against *H. influenzae* is only one dilution lower than the corresponding MIC of azithromycin (MIC 2 $\mu\text{g}/\text{ml}$). Urea (\pm)-**33c** was more potent (MIC 8 $\mu\text{g}/\text{ml}$) than its 3-cladinosyl analogue (\pm)-**11h** (MIC 16 $\mu\text{g}/\text{ml}$) against *Enterococcus faecalis* and **33a** showed the same activity against *E. coli* in comparison to its cladinosyl analogue **11f**. (Bukvić Krajačić et al., 2011a).

Thus, it seems that appropriate linked urea or thiourea moiety at 9a-N of 3-decladinosyl-3-hydroxy- azalides might interact with particular ribosome binding sites and “substitute” the cladinosose sugar interaction. In order to gain more information about that conformational analysis of a compound **35a** was carried out by using systematic conformational search around flexible propyl linker. Analysis of NOE cross peaks in the NOESY spectrum indicated that there is no strong interaction between macrolactone ring and the substituent at 9a-position of **35a**, pointing to the stretched conformations that were also found to be most stable ones in the conformational analysis (Bukvić Krajačić et al., 2011a). Superposed x-ray conformations of ABT-773, (Auerbach et al., 2009), azithromycin (Schlunzen et al., 2003; Hansen et al., 2002), two bound conformations of telithromycin from *Deinococcus radiodurans* (Berisio et al. 2003) and *Haloarcula marismortui* (Hansen et al., 2002) and the lowest conformation for compound **35a** were shown in Fig. 4 (Bukvić Krajačić et al., 2011a).

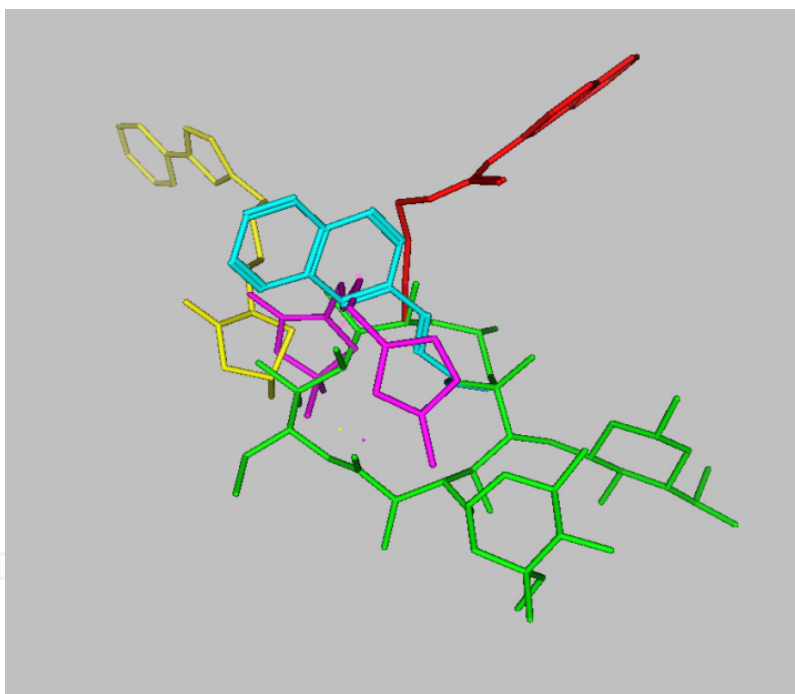


Fig. 4. Superposed x-ray conformations for azithromycin (green) (Hansen et al., 2002), ABT-773 (cyan) (Auerbach et al., 2009), two conformations of telithromycin from *Deinococcus radiodurans* (magenta) (Berisio et al. 2003) and *Haloarcula marismortui* (yellow) (Hansen et al., 2002) complexes and most stable conformation for compound **35a** (red) (Bukvić Krajačić et al., 2011a).

It is clear that substituents at different positions have different spatial arrangements with respect to macrolactone. Until now there is a number of evidence including here mentioned ketolides (Auerbach et al., 2009; Schlunzen et al., 2003; Hansen et al., 2002; Berisio et al., 2003), that high structural diversity is tolerated within the flexible macrolide-binding site of

ribosome. In spite of the knowledge gained so far on macrolide binding, (Novak et al., 2006; Novak et al., 2009; Auerbach et al., 2009; Schlunzen et al., 2003; Hansen et al., 2002; Berisio et al., 2003) an understanding of the mode of their interactions with ribosome still remain incomplete with many issues unresolved. Therefore, it can only be speculated about the possible binding mode of the compound **35a** but it is likely that the additional interaction involving 1-naphthyl-propyl- side-chain, attached at the 9a position, might lead to a further stabilization of a complex with ribosome (Bukvić Krajačić et al., 2011a).

3. Concluding remarks

In summary, the coupling of a arylsulfonyl and benzenesulfonamido moiety to the 9a position of 15-membered azalide scaffold *via* carbamoyl linker has indicated improvement in antibacterial activity of novel azalides.

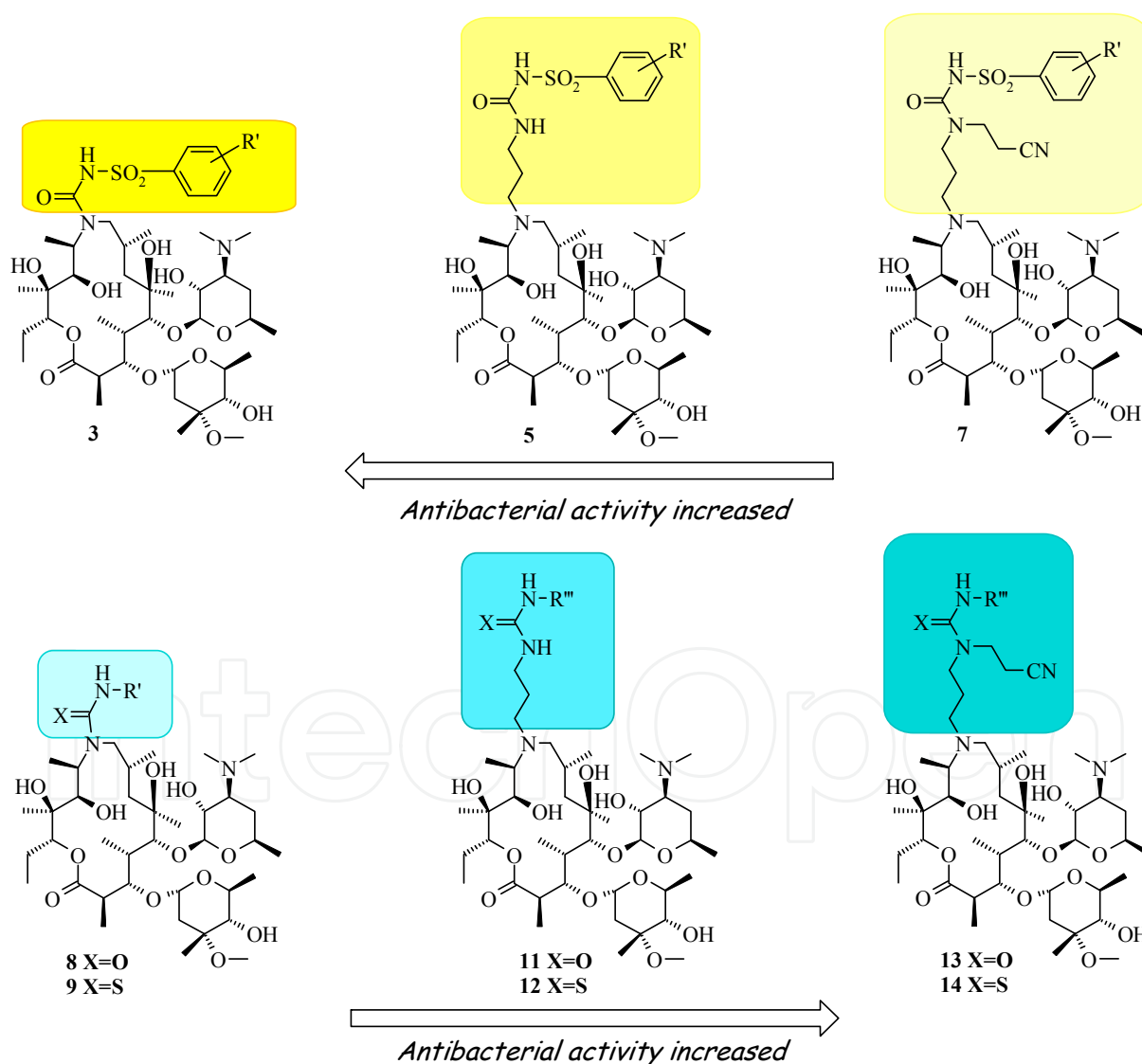


Fig. 5. Antibacterial activities of urea and thiourea derivatives of 15-membered azalides in comparison to sulfonylurea analogues.

Hence, newly synthesised sulfonyl ureas of azalides **3b-3f**, and azalide-sulfonamide conjugates **10a** and **10b** displayed significantly improved activity against inducible resistant *S. pyogenes* strain when compared to azithromycin.

In addition, the introduction of carbamoyl and thiocarbamoyl group at 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 attached at the carbamoyl and thiocarbamoyl group all prepared and tested compounds had high *in vitro* activity against erythromycin susceptible Gram-positive aerobes and Gram-negative microorganisms and especially resistant *S. pyogenes* and *S. pneumoniae* strains. It was also, shown here that urea and thiourea derivatives of 3-decladinosyl-3-hydroxy azalides, although lacking a cladinose sugar, showed noticeable antibacterial activity.

Overall mutual comparison of obtained results can be summarized in three items:

- The observed increase of antibacterial activity in the series of ureas and thioureas **11**, **12**, **13** and **14** (Bukvić Krajačić et al., 2009) in comparison with those of their analogues **8** and **9** (Kujundžić et al., 1995), was opposite to the results obtained for the sulfonylcarbamoyl derivatives **3**, **5** and **7** (Bukvić Krajačić et al., 2005) where a decrease of activity was found when sulfonylcarbamoyl moiety was further away from the azalide ring (Fig. 6)

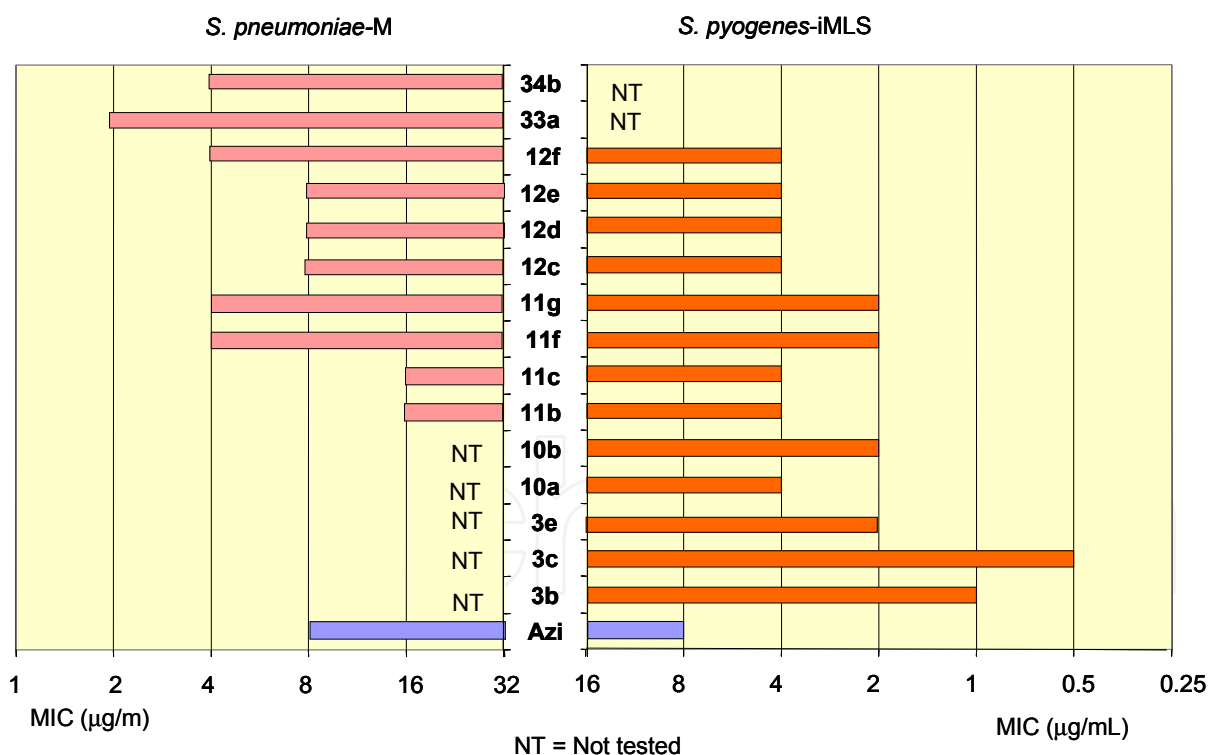


Fig. 6. Antibacterial activity of selected novel sulfonylureas, ureas and thioureas of 15-membered azalides on *S. pneumoniae* efflux-mediated (Bukvić Krajačić et al., 2009) and *S. pyogenes* iMLS (Bukvić Krajačić et al., 2005) resistant strains in comparison to azithromycin

- Several novel sulfonylureas (Bukvić Krajačić et al., 2005), ureas and thioureas (Bukvić Krajačić et al. 2009) of 15-membered azalides showed same or significantly better activity

on *S. pneumoniae* efflux-mediated and *S. pyogenes* iMLS resistant strains in comparison to azithromycin (Fig 7). Among them, new ureas with naphthyl substituents (**11f**, **11g** & **11h**) showed better activity against inducible resistant *S. pyogenes* in comparison to azithromycin. Ureas **11f** & **11g** and thioureas **12c**, **12d**, **12e** and **12f** possess good activity against efflux-mediated resistant *S. pyogenes*, comparable to azithromycin.

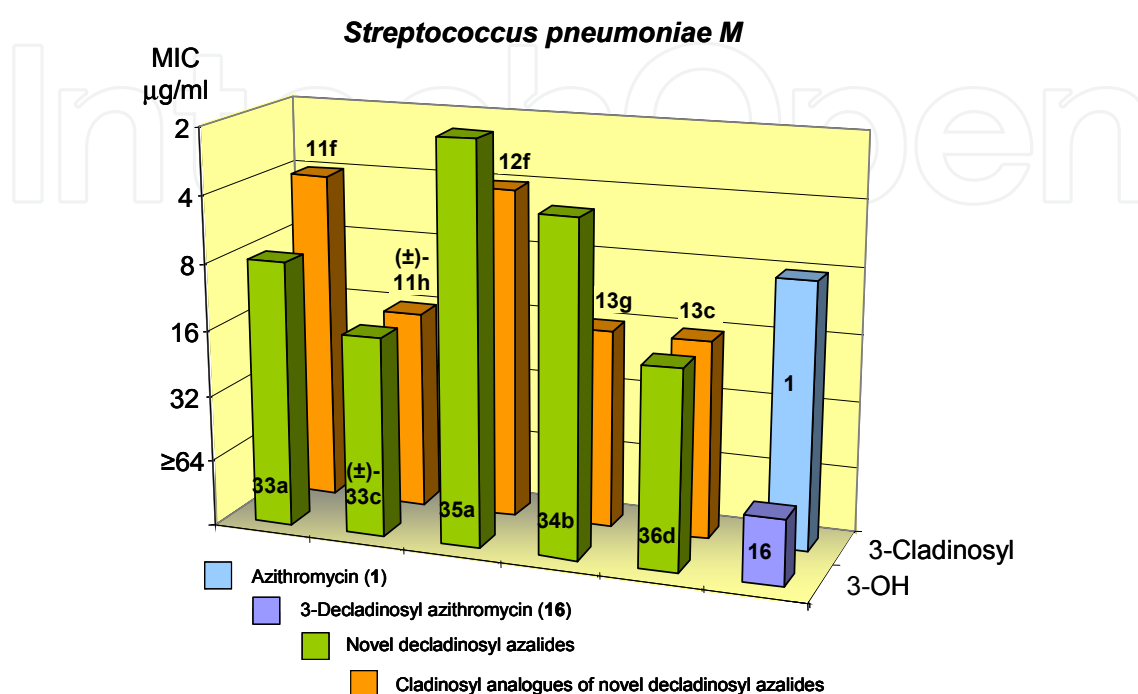


Fig. 7. Antibacterial activity of 3-decladinosyl-3-hydroxy ureas and thioureas on *S. pneumoniae* efflux-mediated resistant strain (Bukvić Krajačić et al., 2011) in comparison to their parent 3-cladinosyl analogues (Bukvić Krajačić et al., 2009) and test standards azithromycin (**1**) and 3-decladinosyl azithromycin (**16**).

- Contrary to the well known fact (LeMahieu, et.al., 1974; Kaneko et.al., 2006; Pal, 2006; Tanikawa, et.al., 2001; Mutak, 2007) and previous results (Bukvić Krajačić et al., 2005, Bukvić Krajačić et al., 2007; Marušić Ištuk et al., 2007), that simple removal of cladinose sugar from macrolides significantly decreases antibacterial activity, unexpectedly, some of the newly discovered 3-decladinosyl-3-hydroxy ureas **33** & **34**, and thioureas **35** & **36** (Bukvić Krajačić et al., 2011) maintain good antibacterial activity against panel of key respiratory Gram-positive and Gram-negative pathogens. Against efflux-mediated resistant *S. pneumoniae* strain they possess comparable or better activity (MIC 2 -16 µg/ml) to their 3-cladinosyl parent analogues **11** & **13** (MIC 4 -16 µg/ml) (Bukvić Krajačić et al., 2009) and azithromycin (**1**) (MIC 8 µg/ml), and significantly better in comparison to the inactive 3-decladinosyl azithromycin (**16**) (MIC >64 µg/ml) (Fig. 7) (Bukvić Krajačić et al., 2011). Also, some 3-decladinosyl-3-hydroxy ureas **33** & **34**, and thioureas **35** & **36**, maintain antibacterial activity against Gram-negative pathogens *H. influenzae* and *M. catarrhalis* in comparison to their parent 3-cladinosyl derivatives (Bukvić Krajačić et al., 2009), and comparable to azithromycin, but demonstrate a large improvement in comparison with inactive 3-decladinosyl azithromycin **16** (Bukvić Krajačić et al., 2011) and other 3-decladinosyl derivatives reported in literature. These small library of 3-decladinosyl-3-hydroxy ureas and thioureas of 15-membered azalides we termed "decladinosylides."

In general, novel sulfonylureas, ureas and thioureas of 15-membered azalides and their 3-decladinosyl-3-hydroxy derivatives 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.

4. Acknowledgements

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5. References

- Agouridas, C.; Denis, A.; Auger, J.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J. F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; Laurin, P.; Martret, O. L.; Loyau, V. & Tessot, N. (1998). Synthesis and Antibacterial Activity of Ketolides (6-O-Methyl-3-oxoerythromycin Derivatives): A New Class of Antibacterials Highly Potent Against Macrolide-Resistant and -Susceptible Respiratory Pathogens. *Journal of Medicinal Chemistry*, Vol. 41, No. 21, (September 1998) pp. 4080-4100, ISSN 0022-2623
- Albrich, W. C.; Monnet, D. L. & Harbarth, S. (2004). Antibiotic Selection Pressure and Resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerging Infectious Diseases*, Vol. 10, No. 3, pp. 514-517, ISSN 1080-6059
- Alihodžić, S.; Fajdetić, A.; Kobrehel, G.; Lazarevski, G.; Mutak, S.; Pavlović, D.; Štimac, V.; Čipčić, H.; Dominis Kramarić, M.; Eraković, V.; Hasenöhr, A.; Maršić, N. & Schönfeld, W. (2006). Synthesis and Antibacterial Activity of Isomeric 15-Membered Azalides. *Journal of Antibiotics*, Vol. 59, No.12, (December 2006), pp. 753-769, ISSN 0021-8820
- Allen, N., (1977). Macrolide Resistance in *Staphylococcus aureus*: Inducers of Macrolide Resistance. *Antimicrobial Agents Chemotherapy*, Vol. 11, (April 1977), pp. 669-674, ISSN 1098-6596.
- Andersen, S. L.; Ager, A. L.; McGreevy, P.; Schuster, B. G.; Ellis, W.; Berman, J. (1994). Efficacy of azithromycin as a causal prophylactic agent against murine malaria. *Antimicrobial Agents Chemotherapy*, Vol. 38, (August 1994). pp. 1862-1863, ISSN 1098-6596
- Andersen, S. L.; Ager, A.; McGreevy, P.; Schuster, B. G.; Wesche, D.; Kuschner, R.; Ohrt, C.; Ellis, W.; Rossan, R.; Berman, J. (1995). Activity of azithromycin as a blood schizonticide against rodent and human plasmodia in vivo. *The American Journal Tropical Medicine and Hygiene*, (February 1995). Vol. 52, pp. 159-161, ISSN 0002-9637
- Anonymous (2000) Heroes of Chemistry Recipients, American Chemical Society Portal, http://portal.acs.org/portal/acs/corg/content?_nfpb=true&_pageLabel=PP_SUPERARTICLE&node_id=1464&use_sec=false&sec_url_var=region1&__uuid=91e8ce27-b8ba-4450-9088-5835121094b4, Sept. 7, 2011).
- Auerbach, T.; Mermershtain, I.; Bashan, A.; Davidovich, C.; Rozenberg, H.; Sherman, D. H.; Yonath, A. (2009). Structural basis for the antibacterial activity of the 12-membered-ring mono-sugar macrolide methymycin *Biotechnologia*, Vol.1, (January 2009), pp. 24-35, ISSN 0860-7796

- Bao, K.; Qiao, F.; Liang, L.; Li, H.; Zhu, H.; Zhang, W. & Wu, Y. (2010). Synthesis and antiproliferative activity of novel erythromycin derivatives. *Medicinal Chemistry Communications*, Vol. 1, No. 4, (August 2010). pp. 294-298, ISSN 2040-2503
- Berisio, R.; Harms, J.; Schlutzen, F.; Zarivach, R.; Hansen, H.A.S.; Fucini, P. & Yonath, A. (2003). Structural Insight into the Antibiotic Action of Telithromycin against Resistant Mutants. *Journal of Bacteriology*, Vol. 185, No. 14, (May 2003), pp. 4276-4279, ISSN 0021-9193
- Bright, G. M. (Pfizer), (1984). Antibacterial N-methyl 11-aza-10-deoxo-10-dihydroerythromycin A and pharmaceutically acceptable acid addition salts thereof, intermediates therefore, and processes for their preparation. US 4 474 768, Oct. 2, 1984 (US Prior. Nov. 15, 1982).
- Bright, G. M.; Nagel, A. A.; Bordner, J.; Watrous, K. A.; Sciavolino, F. C.; English, A. R.; Retsema, J. A.; Anderson, M. R.; Brennan, L. A.; Borovoy, R. J.; Cimochowski, C. R.; Faiella, J. A.; Girard, A. E.; Girard, D.; Herbert, C.; Manousos, M. & Mason, R. (1988). Synthesis, *in vitro* and *in vivo* activity of novel 9-deoxo-9a-aza-9a-homoerythromycin A derivatives; a new class of macrolide antibiotics, the azalides. *Journal of Antibiotics*, Vol. 41: No. 8, (February 1988), pp. 1029-1047, ISSN 0021-8820
- Bukvić Krajačić, M.; Kujundžić, N.; Dumić, M.; Cindrić, M.; Brajša, K.; Metelko, B. & Novak, P. (2005). Synthesis, Characterization and *in vitro* Antimicrobial Activity of Novel Sulfonylureas of 15-Membered Azalides. *Journal of Antibiotics*, Vol. 58, No.6, (June 2005), pp. 380-389, ISSN 0021-8820
- Bukvić Krajačić, M.; Novak, P.; Cindrić, M.; Brajša, K.; Dumić, M. & Kujundžić, N. (2007). Azithromycin-sulfonamide conjugates as inhibitors of resistant *Streptococcus pyogenes* strains. *European Journal of Medicinal Chemistry*, Vol. 42 No. 2, (February 2007), pp. 138-145, ISSN 0223-5234
- Bukvić Krajačić, M.; Novak, P.; Dumić, M.; Cindrić, M.; Čipčić Paljetak, H. & Kujundžić, N. (2009). Novel ureas and thioureas of 15-membered azalides with antibacterial activity, against key respiratory pathogens. *European Journal of Medicinal Chemistry*, Vol. 44, No. 9, (September 2009), pp. 3459-3470, ISSN 0223-5234
- Bukvić Krajačić, M.; Dumić, M.; Novak, P.; Cindrić, M.; Koštrun, S.; Fajdetić, A.; Alihodžić, S.; Brajša, K. & Kujundžić, N. (2011a) Discovery of Novel Ureas and Thioureas of 3-Decladinosyl-3-hydroxy 15-Membered Azalides Active Against Efflux-mediated Resistant *Streptococcus Pneumoniae*. *Bioorganic & Medicinal Chemistry Letters*, Vol. 21 No. 2, (January 2011), pp. 853-856, ISSN 0960-894X
- Bukvić Krajačić, M.; Perić, M.; Smith, K. S.; Ivezić Schönfeld, Z.; Žiher, D.; Fajdetić, A.; Kujundžić, N.; Schönfeld, W.; Landek, G.; Jelić, D.; Ager, A.; Milhous, W. K.; Ellis, W.; Spaventi, R. & Ohrt, C. (2011b). Synthesis, Structure-Activity Relationship and Antimalarial Activity of Ureas and Thioureas of 15-membered Azalides. *Journal of Medicinal Chemistry*, Vol. 54, No. 10, (April 2011), pp. 3595-3605, ISSN 0022-2623
- Čulić, O.; Bosnar, M.; Marjanovic, N.; Erakovic, V.; Jelic, D. & Verbanac, D. (2006). 9A-Carbamoyl and Thiocarbamoyl azalides with anti-inflammatory activity PCT Int. Appl. WO 2006097849 A1 20060921.
- Čulić, O.; Eraković, V. & Parnham, M. (2001). Anti-inflammatory effects of macrolide antibiotics, *European Journal of Pharmacology*, Vol. 429, No. 1-3, (October), pp.209-229 ISSN: 0014-2999

- M. L. Cohen, M. L. (1992). Epidemiology of Drug Resistance: Implications for a Post—Antimicrobial Era, *Science*, Vol. 257, No. 5073 (August 1992), pp. 1050-1055; ISSN: 0036-8075
- Cruzan, S. (2007). FDA Announces Label and Indication Changes for the Antibiotic Ketek, February 12, 2007 <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108842.htm> (Sept. 8, 2011)
- Cunningham, M. W. (2000). Pathogenesis of Group A streptococcal infections. *Clinical Microbiology Review*, Vol. 13, pp. 470-511, ISSN 0983-8512
- Djokić, S.; Kobrehel, G.; Lazarevski, G.; Lopotar, N.; Tamburašev, Z.; Kamenar, B.; Nagl, A. & Vicković, I. (1986). Erythromycin series. Part 11. Ring expansion of erythromycin A oxime by the Beckmann rearrangement. *Journal of Chemical Society, Perkin Trans. I* (January 1986) pp. 1881-1990 ISSN 1472-7781
- Djokić, S. Kobrehel, G. & Lazarevski, G. (1987). Erythromycin series XII. Antibacterial *in vitro* evaluation of 10-dihydro-10-deoxo-11-azaerythromycin A: synthesis and structure activity relationship of its acyl derivatives. *Journal of Antibiotics*, Vol. 40, pp. 1006-1015; ISSN 0021-8820
- Djokić, S; Kobrehel, G.; Lopotar, N.; Kamenar, B.; Nagl, A. & Mrvoš, D. (1988). Erythromycin series. Part 13. Synthesis and structure elucidation of 10-dihydro-10-deoxo-11-methyl-11-azaerythromycin A. *Journal of Chemical Research (S)*, pp. 152~153, *ibid.*, Miniprint, pp. 1239-1257, ISSN 0308-2342
- Elliott, R. L.; Pireh, D.; Griesgraber, G.; Nilius, A. M.; Ewing, P. J.; Bui, M. H.; Raney, P. M.; Flamm, R. K.; Kim, K.; Henry, R.F.; Chu, D. T. W.; Plattner, J. J. & Or, Y. S. (1998) Anhydrolide Macrolides. 1. Synthesis and Antibacterial Activity of 2,3-Anhydro-6-O-methyl 11,12-Carbamate Erythromycin A Analogues. *Journal of Medicinal Chemistry*, Vol. 41, No. 10, (April 1998), pp. 1651-1659, ISSN 0022-2623
- Fajdetić, A.; Čipčić Paljetak, H.; Lazarevski, G.; Hutinec, A.; Alihodžić, S.; Đerek, M.; Štimac, V.; Andreotti, D.; Šunjić, V.; Berge, J.M.; Mutak, S.; Dumić, M.; Lociuro, S.; Holmes, D.J.; Maršić, N.; Eraković Haber, V. & Spaventi R., (2010). 4"-O-(ω -Quinolylamino-alkylamino)propionyl derivatives of selected macrolides with the activity against the key erythromycin resistant respiratory pathogens, *Bioorganic and Medicinal Chemistry*, Vol. 18, No. 17, (September 2010), pp. 6559-6568, ISSN: 09680896
- Fajdetić, A.; Vinter, A.; Čipčić Paljetak, H.; Padovan, J.; Palej Jakopović, I.; Kapić, S.; Alihodžić, S.; Filić, D.; Modrić, M.; Košutić-Hulita, N.; Antolović, R.; Ivezić Schönfeld, Z.; Mutak, S.; Eraković Haber, V. & Spaventi R. Synthesis, activity and pharmacokinetics of novel antibacterial 15-membered ring macrolones, *European Journal of Medicinal Chemistry* Vol.46, No. 8, (August 2011), pp. 3388-3397, ISSN: 0223-5234
- Farrell, D. J.; Castanheira, M.; Sader, H. S. & Jones, R. N. (2010). The *in vitro* evaluation of solithromycin (CEM-101) against pathogens isolated in the United States and Europe (2009), *Journal of Infection* Vol. 61, No. 6 (December 2010), pp. 476-483; ISSN 0163-4453
- Girard, A. E.; Girard, D.; English, A. R.; Gotz, T. D.; Cimochoowski, C. R.; Faiella, J. A.; Haskell, S. L. & Retsema, J. A (1987). Pharmacokinetic and *in vivo* studies with azithromycin (CP-62,993), a new macrolide with an extended half life and excellent

- tissue distribution. *Antimicrobial Agents Chemotherapy*, Vol. 31, (December 1986), pp. 1948-1954, ISSN 1098-6596
- Granizo, J.J.; Aguilar, L.; Casal, J.; Dal-Ré, R. & Baquero F. (2000). *Streptococcus pyogenes* resistance to erythromycin in relation to macrolide consumption in Spain (1986-1997). *Journal of Antimicrobial Chemotherapy*, Vol. 46, pp. 959-964, ISSN 1460-2091
- Hansen, G. T.; Metzler, K. L.; DeCarolus, E. & Blondeau, J.M.; (2002). The macrolides, *Expert Opin. Investig. Drugs*, Vol. 11, No. 2, (Feb. 2002), pp. 189-215, ISSN 1354-3784, eISSN 1744-7658.
- Hansen, J. L.; Ippolito, J. A.; Ban, N.; Nissen, P.; Moore, P. B.; Steitz, T. A. (2002). The Structures of Four Macrolide Antibiotics Bound to the Large Ribosomal Subunit. *Molecular Cell*, Vol. 10, No. 1, (July 2002), pp. 117-128, ISSN 1097-2765
- Hutinec, A.; Djerek, M.; Lazarevski, G.; Šunjić, V.; Čipčić Paljetak, H.; Alihodžić, S. Eraković Haber, V.; Dumić, M.; Maršić N. & Mutak S. (2010). Novel 8a-aza-8a-homoerythromycin-4''-(3-substituted-amino)propionates with broad spectrum antibacterial activity, *Bioorganic and Medicinal Chemistry Letters* Vol. 20, No. 11 (June 2010), pp. 3244-3249; ISSN: 0960-894X
- Hutinec, A.; Rupčić, R.; Žiher, D.; Smith, K. S.; Milhous, W. ; Ellis, W. ; Ohrt, C. & Ivezić Schönfeld, Z. (2011). An automated, polymer-assisted strategy for the preparation of urea and thiourea derivatives of 15-membered azalides as potential antimalarial chemotherapeutics. *Bioorganic and Medicinal Chemistry*, Vol. 19, No. 5, (March 2011), pp. 1692-1701, ISSN 0968-0896
- Kaneko, T., Dougherty, T.J. & Magee, T.V. (2006). Macrolide Antibiotics, In: *Comprehensive Medicinal Chemistry II*, D. Triggle, J. Taylor, J. Plattner, M. C. Desai (Eds.), Vol. 7 pp. 519-566, Therapeutic Areas II, Elsevier, ISBN 0-08-044513-6
- Kapić, S.; Čipčić Paljetak, H.; Alihodžić, S.; Antolović, R.; Eraković Haber, V.; Jarvest, R. L.; Holmes, D. J.; Broskey, J. P. & Hunt, E. (2010). 6-Alkylquinolone-3-carboxylic acid tethered to macrolides synthesis and antimicrobial profile, *Bioorganic and Medicinal Chemistry*, Vol. 18, No. 17, (September 2010), pp. 6569-6577, ISSN 0968-0896
- Kapić, S.; Fajdetić, A.; Koštrun, S.; Čikoš, A.; Čipčić Paljetak, H.; Antolović, R.; Holmes, D. J. & Alihodžić, S., (2011a). Synthesis and Activity of New Macrolones: Conjugates Between 6(7)-(2'-Aminoethyl)-amino-1-cyclopropyl-3-carboxylic acid (2'-hydroxyethyl) amides and 4''-Propenoyl-azithromycin, *Bioorganic and Medicinal Chemistry*, In Press, Accepted Manuscript, doi: 10.1016/j.bmc.2011.07.011; Accepted Date: 8 July 2011; ISSN 0968-0896
- Kapić, S.; Čipčić Paljetak, H.; Palej Jakopović, I.; Fajdetić, A.; Ilijaš, M.; Štimac, V.; Brajša, K.; Holmes, D. J. ; Berge, J. & Alihodžić, S. (2011b). Synthesis of macrolones with central piperazine ring in the linker and its influence on antibacterial activity *Bioorganic and Medicinal Chemistry*, In Press, Accepted Manuscript, doi: 10.1016/j.bmc.2011.07.010; Accepted Date: 8 July 2011; ISSN 0968-0896
- Kirst, H. A. (1996a). Expanding the Role of Macrolide Compounds as Therapeutic Agent, In: *Studies in Medicinal Chemistry* Choudhary, M. I. (Ed.), Vol. 1, Harwood Academic Publisher, Amsterdam, pp. 1-47, ISBN: 978-0-444-51572-8
- Kirst, H. A. (1996b). Aminoglycoside, Macrolide, Glycopeptide, and Miscellaneous Antibacterial antibiotics, in: Wolf M. E. (Ed.), *Burger's Medicinal Chemistry and Drug Discovery*, Fifth Ed., Vol. 2, Ch. 32, Wiley Interscience, New York, 1996, pp. 463-525; ISBN 0-471 57557-7.

- G. Kobrehel, G. & S. Djokić, S. (PLIVA), (1982). Nouveaux derives de l'erythromycine A, procede pour leur preparation et leur utilisation comme substances antibacteriennes, BE 892 357, July 1, 1982, (YU Prior. March 6, 1981)
- Kobrehel, G.; Radobolja, G.; Tamburašev, Z.; & Djokić, S. (PLIVA), (1982). 11-Aza-10-deoxy-10-dihydroerythromycin A and derivatives thereof as well a process for their preparation. US 4 328 334 (1982)
- Kobrehel, G. & Djokić, S. (PLIVA) (1985). 11-Methyl-11-aza-4-O-cladinosyl-6-O-desosaminy-15-ethyl-7,13,14-trihydroxy-3,5,7,9,12,14-hexamethyl-oxacyclopentadecane-2-one and derivatives thereof. US 4 517 359, (May 14, 1985)
- Kujundžić, N.; Kobrehel, G.; Banić, Z.; Kelnerić, Z. & Kojić-Prodić, B. (1995) Azalides: Synthesis and antibacterial activity of novel 9a-N-(N'-substituted carbamoyl and thiocarbamoyl) derivatives of 9-deoxy-9a-aza-9a-homoerythromycin A. *European Journal of Medicinal Chemistry*, Vol. 30, (January 1995), pp. 455-462, ISSN 0223-5234
- Kuschner, R. A.; Heppner, D. G.; Andersen, S. L.; Wellde, B. T.; Hall, T.; Schneider, I.; Ballou, W. R.; Foulds, G.; Sadoff, J. C. & Schuster, B. (1994). Azithromycin prophylaxis against a chloroquine-resistant strain of Plasmodium falciparum. *Lancet*, Vol. 343, No. 8910, pp. 1396-1397, ISSN 0140-6736
- Labro, M.-T. (2000). Interference of Antibacterial Agents with Phagocyte Functions: Immunomodulation or "Immuno-Fairy Tales"?. *Clinical Microbiology Review*, Vol. 13, (October 2000), pp. 615 - 650, ISSN: 1098-6618.
- Labro, M.-T. (2004). Macrolide antibiotics: current and future uses, *Expert Opinion in Pharmacotherapy*. Vol. 5, No. 3 (March 2004), pp. 541-550, ISSN: 1465-6566
- Lee, Y.; Choi, J. Y.; Fu, H.; Harvey, C.; Ravindran, S.; Roush, W. R.; Boothroyd, J. C. & Khosla, C. (2011). Chemistry and Biology of Macrolide Antiparasitic Agents, *Journal of Medicinal Chemistry*. Vol. 54, No. 8 (April 2011), pp 2792-2804, ISSN 0022-2623
- LeMahieu, R. A.; Carson, M.; Kierstead, R. W.; Fern, L. M. & Grunberg E. (1974). Glycoside cleavage reactions on erythromycin A. Preparation of erythronolide A. *Journal of Medicinal Chemistry*. (September 1974), Vol. 17, No. 9, pp. 953-956, ISSN 0022-2623
- Marušić-Ištuk, Z.; Kujundžić, N.; Kobrehel, G; Mutak, S & Maršić, N. (2000). Halo derivatives of 9-deoxy-9a-aza-9a-homoerythromycin A. WO 00/66603, November 9 2000
- Marušić Ištuk, Z.; Mutak, S.; Kujundžić, N. & Kragol, G. (2007). Novel 9a-carbamoyl- and 9a-thiocarbamoyl-3-decladinosyl-6-hydroxy and 6-methoxy derivatives of 15-membered macrolides. *Bioorganic and Medicinal Chemistry*, (April 2007), Vol. 15, 4498-4510, ISSN 09680896
- Marušić Ištuk, Z.; Čikoš, A.; Gembarovski, D.; Lazarevski, G.; Djilović, I.; Matković-Čalogović, D. & Kragol, G. (2011). Novel 9a,11-bridged azalides: One-pot synthesis of N'-substituted 2-imino-1,3-oxazolidines condensed to an azalide aglycone, *Bioorganic and Medicinal Chemistry* Vol. 19, No. 1, (January 2011), pp. 556-566; ISSN 0968-0896
- Matanović Škugor, M.; Štimac, V.; Palej, I.; Lugarić, D.; Čipčić Paljetak, H.; Filić, D., Modrić, M.; Đilović, I.; Gembarovski, D.; Mutak, S.; Eraković Haber, V.; Holmes, D. J.; Ivezić-Schönfeld, Z. & Alihodžić, S. (2010). Synthesis and biological activity of 4''-O-acyl derivatives of 14- and 15-membered macrolides linked to ω-quinolone-carboxylic unit, *Bioorganic & Medicinal Chemistry*, Vol. 18, No. 17 (September 2010), pp. 6547-6558; ISSN 0968-0896

- Mutak, S. (2007). Azalides from Azithromycin to New Azalide Derivatives. *Journal of Antibiotics*, Vol. 60, No. 2, (January 2007), pp. 85–122, ISSN 0021-8820
- Mwakwari, S. C.; Guerrant, W.; Patil, V.; Khan, S. I.; Tekwani, B. L.; Gurard-Levin, Z. A.; Mrksich, M. & Oyelere, A. K. (2010). Non-Peptide Macrocyclic Histone Deacetylase Inhibitors Derived from Tricyclic Ketolide Skeleton, *Journal of Medicinal Chemistry*, Vol. 53, No. 16, (August 2010), pp 6100–6111; ISSN 0022-2623
- Nagai, K.; Appelbaum, P. C.; Davies, T. A.; Kelly, L. M. ; Hoellman, D. B. ; Tambic Andrasevic, A.; Drukalska, L.; Hryniewicz, W. ; Jacobs, M. R.; Kolman, J.; Miciuleviciene, J.; Pana, M.; Setchanova, L.; Konkoly Thege, M.; Hupkova, H.; Trupl, J. & Urbaskova, P. (2002). Susceptibility to Telithromycin in 1,011 *Streptococcus pyogenes* Isolates from 10 Central and Eastern European Countries. *Antimicrobial Agents Chemotherapy*, Vol. 46, No. 2, pp. 546-549, ISSN 1098-6596
- Nakajima, Y. (1999). Mechanisms of bacterial resistance to macrolide antibiotics. *Journal Infection and Chemotherapy*, Vol. 5, pp. 61-74, ISSN 1341-321X
- Novak, P.; Tatić, I.; Tepeš, P.; Koštrun, S. & Barber, J. (2006). Systematic Approach to Understanding Macrolide-Ribosome Interactions: NMR and Modeling Studies of Oleandomycin and Its Derivatives. *Journal of Physical Chemistry A*, Vol. 110, No. 2, (August 2006), pp. 572-579, ISSN 1089-5639
- Novak, P.; Barber, J.; Čikoš, A.; Arsić, B.; Plavec, J.; Lazarevski, G.; Tepeš, P. & Košutić-Hulita, N. (2009). Free and bound state structures of 6-O-methyl homoerythromycins and epitope mapping of their interactions with ribosomes. *Bioorganic & Medicinal Chemistry*, Vol. 17, No. 16, (August 2009), pp. 5857-5867, ISSN 09680896
- Ohrt, C.; Willingmyre, G. D.; Lee, P.; Knirsch, C. & Milhous, W. (2002). Assessment of azithromycin in combination with other antimalarial drugs against *Plasmodium falciparum* in vitro. *Antimicrobial Agents Chemotherapy*, Vol. 46, (August 2002), pp. 2518-2524, ISSN 1098-6596
- Oyelere, A. K.; Chen, P. C.; Guerrant, W.; Mwakwari, S. C.; Hood, R.; Zhang Y. & Fan, Y. (2009). Non-Peptide Macrocyclic Histone Deacetylase Inhibitors, *Journal of Medicinal Chemistry*, Vol. 52, No. 2, (January 2009), pp 456–468; ISSN 0022-2623
- Pal, S. (2006). A journey across the sequential development of macrolides and ketolides related to erythromycin. *Tetrahedron*, Vol. 62, No. 14, (April 2006), pp. 3171–3200, ISSN: 0040-4020
- Palej Jakopović, I.; Kragol, G.; Forrest, A. K.; Frydrych, C. S.V.; Štimac, V.; Kapić, S.; Matanović Škugor, M.; Ilijaš, M.; Čipčić Paljetak, H.; Jelić, D.; Holmes, D. J.; Hickey, D. M.B.; Verbanac, D.; Eraković Haber, V. & Alihodžić, S. (2010) Synthesis and properties of macrolones characterized by two ether bonds in the linker. *Bioorganic and Medicinal Chemistry*, Vol. 18, No. 17, (September 2010), pp. 6578-6588, ISSN: 09680896
- Pavlović, D.; Fajdetić, A. & Mutak, S. (2010). Novel hybrids of 15-membered 8a- and 9a-azahomoerythromycin A ketolides and quinolones as potent antibacterials. *Bioorganic and Medicinal Chemistry*, Vol. 18, No. 24, (December 2010), pp. 8566-8582, ISSN: 09680896
- Pavlović D. & Mutak, S. (2011). Discovery of 4"-Ether Linked Azithromycin-Quinolone Hybrid Series: Influence of the Central Linker on the Antibacterial Activity, *ACS Med. Chem. Lett.*, Vol. 2, No. 5 (May 2011), pp 331-336; ISSN: 1948-5875

- Pestka, S. & LeMahieu, R. (1974a). Inhibition of [14C]Chloramphenicol Binding to *Escherichia coli* Ribosomes by Erythromycin Derivatives. *Antimicrobial Agents Chemotherapy*, Vol. 6, (July 1974), pp. 39-45, ISSN 1098-6596
- Pestka, S. & Lemahieu, R. A. (1974b). Effect of Erythromycin Analogues on Binding of [14C]Erythromycin to *Escherichia coli* Ribosomes *Antimicrobial Agents Chemotherapy*, Vol. 6, (October 1974), pp. 479-488, ISSN 1098-6596.
- Pestka, S.; Lemahieu, R. A. & Miller, P. (1974). Correlation of Effects of Erythromycin Analogues on Intact Bacteria and on [14C]Erythromycin Binding to *Escherichia coli* Ribosomes. *Antimicrobial Agents Chemotherapy* Vol. 6, (October 1974), pp. 489-491, ISSN 1098-6596.
- Pestka, S.; Vince, R.; LeMahieu, R.; Weiss, F.; Fern, L.; Unowsky, J. (1976). Induction of Erythromycin Resistance in *Staphylococcus aureus* by Erythromycin Derivatives. *Antimicrobial Agents Chemotherapy*, Vol. 9, (January 1976), pp. 128-130, ISSN 1098-6596
- Poehlsgrard, J. & Douthwaite, S. (2003). Macrolide antibiotic interaction and resistance on the bacterial ribosome. *Current Opinion in Investigational Drugs*, Vol. 4, pp. 140-144, ISSN 1472-4472
- Prieto, J.; Calvo, A. & Gómez-Lus M. L. (2002). Antimicrobial resistance: a class effect?. *Journal of Antimicrobial Chemotherapy*, Vol. 50 (Suppl. S2), pp. 7-12, ISSN 1460-2091
- Retsema, J.; Girard, A.; Schelkly, W.; Manousos, M.; Anderson, M.; Bright, G.; Borovoy, R.; Brenan, L. & Manson R. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against Gram-negative organisms. *Antimicrobial Agents Chemotherapy*, Vol. 31, (December 1986), pp. 1939-1947, ISSN 1098-6596
- Romano, M. F.; Avellino, R.; Petrella, A.; Bisogni, R.; Romano, S. & Venuta, S. (2004). Rapamycin inhibits doxorubicin-induced NF- κ B/Rel nuclear activity and enhances the apoptosis of melanoma cells. *European Journal of Cancer*, (December 2004) Vol. 40, No. 16, pp. 2829-2836, ISSN 0959-8049
- Schlunzen, F.; Harms, J. M.; Franceschi, F.; Hansen, H. A.; Bartels, H.; Zarivach, R. & Yonath, A. (2003) Structural Basis for the Antibiotic Activity of Ketolides and Azalides. *Structure*, Vol. 11, No. 3, pp. 329-338, ISSN 0969-2126
- Schönfeld W. & Kirst H. A. (Eds.), (2002). *Macrolide Antibiotics*, Birkhäuser Verlag, Basel, ISBN: 978-0-12-526451-8
- Schönfeld, W. & Mutak S., (2002). Azithromycin and Novel Azalides In: *Macrolide Antibiotics*, Schönfeld, W.; Kirst H. A. (Eds.), pp. 73-95, Birkhäuser Verlag, Basel, ISBN: 978-0-12-526451-8,
- Schönwald, S.; Škerk, V.; Petričević, I.; Cart, V.; Majerus-Mišić, L. & Gunjača, M. (1991). Comparison of three-day and five-day courses of azithromycin in the treatment of atypical pneumonia. *European Journal of Clinical Microbiology and Infectious Diseases*, Vol. 10, pp. 877-880, ISSN 0934-9723
- Sheldrick, G.M.; Kojić-Prodić; B., Banić; Z., Kobrehel; G. & Kujundžić, N. (1995). Structure of 9-deoxy-9a-N-(N'-(4'-pyridyl)carbamoyl)-9a-aza-9a-homoerythromycin A and conformational analysis of analogous 9a-aza 15-membered azalides in solid state. *Acta Crystallographica B51*, Part. 3, (June 1995), pp. 358-366, eISSN 1600-5740
- Sidhu, A. B.; Sun, Q.; Nkrumah, L. J.; Dunne, M. W.; Sacchetti, J. C. & Fidock, D. A. (2007). In vitro efficacy, resistance selection, and structural modeling studies implicate the

- malarial parasite apicoplast as the target of azithromycin. *Journal Biological Chemistry*, Vol. 282, (November 2006), pp. 2494-2504, ISSN 0021-9258
- Spaventi, R. (2002). R&D Challenges for the Future, PLIVA R & D booklet, PLIVA Zagreb 2002 (<http://www.pliva.com/press/news/article/665/RD-Challenges-for-the-Future.html>; Sept. 6, 2011)
- Steinmeyer, A. (2006). The hit-to-lead process at Schering AG: strategic aspects. *ChemMedChem.*, Vol. 1, pp. 31-36, ISSN 1860-7187
- Štimac, V.; Matanović Škugor, M.; Palej Jakopović, I.; Vinter, A.; Ilijaš, M.; Alihodžić S. & Mutak S. (2010). Initial Scale-Up and Process Improvements for the Preparation of a Lead Antibacterial Macrolone Compound, *Organic Process Resesearch and Development*, Vol. 14, No. 6, (November 2010), pp 1393-1401 ISSN: 1083-6160
- Sunazuka, T.; Omura, S.,; Iwasaki, S.; Ōmura, S. (2002). Chemical Modification of Macrolides, In *Macrolide Antibiotics, Chemistry, Biology and Practice*, 2nd. Ed., Ōmura S., (Ed.), Academic Press, New York, pp. 99- 180; ISBN 978-0-12-526451-8
- Sutcliffe, J.; Tait-Kamradt, A. & Wondrack, L. (1996). *Streptococcus pneumoniae* and *Streptococcus pyogenes* resistant to macrolides but sensitive to clindamycin: a common resistance pattern mediated by an efflux system. *Antimicrobial Agents Chemotherapy*, Vol. 40, pp. 1817-24, ISSN 1098-6596
- Szczypa, K.; Sadowy, E.; Izdebski, R. & Hryniewicz, W. (2004). A rapid increase in macrolide resistance in *Streptococcus pyogenes* isolated in Poland during 1996-2002. *Journal of Antimicrobial Chemotherapy*, Vol. 54, pp. 828~831, ISSN 1460-2091
- Takanashi, H. & Cynshi, O. (2009). Motilides: A long and winding road: Lessons from mitemcinal (GM-611) on diabetic gastroparesis, *Regulatory Peptides*, Vol. 155, No. 1-3, (June 2009), pp, 18-23; ISSN: 0167-0115
- Tanikawa, T.; Asaka, T.; Kashimura, M.; Misawa, Y.; Suzuki, K.; Sato, M.; Kameo, K.; Morimoto, S. & Nishida, A. (2001). Synthesis and Antibacterial Activity of Acylides (3-O-Acyl-erythromycin Derivatives): A Novel Class of Macrolide Antibiotics. *Journal of Medicinal Chemistry*, (October 2001), Vol. 44, No. 24, pp. 4027-4030, ISSN 0022-2623.
- Tanikawa, T.; Asaka, T.; Kashimura, M.; Suzuki, K.; Sugiyama, H.; Sato, M.; Kameo, K.; Morimoto, S. & Nishida, A. (2003). Synthesis and Antibacterial Activity of a Novel Series of Acylides: 3-O-(3-Pyridyl)acetylerythromycin A Derivatives. *Journal of Medicinal Chemistry*, Vol. 46, No. 13 (May 2003), pp. 2706-2715, ISSN 0022-2623
- Travis, J. (1994). Reviving the Antibiotic Miracle? *Science*, Vol. 264, No. 5157 (April 1994), pp. 360-362; ISSN: 0036-8075
- Vanaudenaerde, B. M.; Meyts, I.; Vos, R.; Geudens, N. ; De Wever, W.; Verbeken, E.K. ; VanRaemdonck, D.E.; Dupont, L.J. & Verleden, G.M. (2008). A dichotomy in bronchiolitis obliterans syndrome after lung transplantation revealed by azithromycin therapy. *Eurropean Respiratory Journal*, Vol. 32, No. 4, (October 2008), pp 832-843, ISSN: 0903-1936
- Van Bambeke, F.; Harms, J. M.; Van Laethem, Y.; Tulkens, P. M. (2008). Ketolides: pharmacological profile and rational positioning in the treatment of respiratory tract infections. *Expert Opinion in Pharmacotherapy* Vol. 9, No. 2, (January 2008), pp. 267-283, ISSN 1465-6566
- Weisblum, B. (1998). Macrolide resistance. *Drug Resistance Updates*, Vol. 1, pp. 29-41, ISSN 1368-7646

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