A review study on chemistry and biology of macrolide antibiotics

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Abstracts.

Macrolide antibiotics are the most important antibiotics used among clinically, which are protein synthesis inhibitors e.g. Erythromycin, Clarithromycin, Azithromycin, Fidaxomicin,Solithromycin,Spiramycin,Troleandomycin ,Tylosin/tylocine ,Roxithromycin and Telithromycin have been used primarily in treatment ofinfectiousdiseasesof respiratory systems which are caused by gram-positive bacteria, gram-negative bacteria and also used as antifungal drugs. Erythromycin, discovered in 1952 from *Streptomyces erythreus* was the first macrolides antibiotics and was widely used for those patients which had been allergic to penicillin or were suffering from penicillin-resistant illnesses.The mechanism of action of macrolide antibiotics are bacteriostatic i.e. they inhibit/suppress the growth of bacteria instead of killing bacteria completely by inhibiting the biosynthesis of bacterial proteins by disturbing with ribosome function, and this inhibitory mechanisms of macrolides has been proved by the structure of the ribosome–macrolide complexes study by x-ray crystallography methods. They are broad spectrum antibiotics and have been found to be relatively safe. Chemically, the macrolides belongs to natural products and its structure contains a large macrocyclic usually 14 to16-memberedlactone ring to which one or more deoxysugars, called as usually *cladinose* and *desosamine* moieties, can belinked.

The semisynthetic macrolides *Clarithromycin and Azithromycin* which are commonly referred as second-generation macrolides were synthesized from *Erythromycin*, are a broader spectrum of activity as well as showing improvement in pharmacokinetic properties. But the exhaustive use of these antibiotics had also increased the resistivity among various strains viz. *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*of bacteria. So third-generation macrolides., known as the ketolides, i.e.*Telithromycin, Cethromycin, and Solithromycin*which are structurally related to other macrolidesand effective against these resistant bacterial strains have been developed. These synthetic macrolides have shown

increased affinity for the bacterial ribosome as well as a diminished affinity to be efflux pump substrates as compared with the 1st and 2nd generation macrolides. In this review the current knowledge about macrolides antibiotics their syntheses, their mechanism and mode of action bybinding to the 50S subunit of ribosomes of bacteria of macrolides , mechanisms ofresistance developed by the bacteria against macrolides viz., *Erythromycin, Clarithromycin and Azithromycin*, and their pharmacokinetic study have been are reviewed. The two mechanisms of macrolide resistances by the bacterial strains have been proposed. The first mechanism is due to inducible expression of bacterial enzymeactivity in methyltransferase. While, the second methods of resistance has been found to be mediated by nascent peptideswhich interactspecifically with the macrolides bounded ribosome complex.There is also closeness between these twomechanisms withthe common mode of macrolide action, i.e. binding to 50S subunit of ribosomes, which has also been discussed in this review.

Keywords: *Macrolides Antibiotics*, *Erythromycin Azithromycin,* ketolides, Protein synthesis, and resistance.

Introduction.

The macrolides antibiotics which have been produced by Streptomyces species of fungi are a large family of antimicrobials, antifungal agents with established efficacy, efficiency as well as a good tolerability profile. At present time the available macrolides are found to be well tolerated, in available oral formulation and so, these are widely used in treatment ofbacterial infections of mild-to-moderate ranges.

Because of these merits they are frequently used in the treatment of bacterial infection of respiratory tract (RTIs), body cavity infection, and soft tissues infection. Macrolides antibiotics are primarily are bacteriostatic i.e., they restrict or inhibit the growth of bacteria rather than bactericidal i.e. killing the bacteria mainly by inhibiting the protein synthesis.Macrolides antibiotic are generally effective against infections caused by the gram-positive bacteria (e.g., Streptococcus pneumoniae) and some specific gram-negative bacteria (e.g., Bordetella pertussis, Haemophilusinfluenzae). They have been used against following medical conditions viz., Babesiosis (A rare, often severe infection caused by protozoa of the genus.), in bacterial endocarditis prevention (caused by the direct invasion of bacteria) ,Bartonellosis(by bacteria of the genus Bartonella), Bronchitis, ,*Campylobacter Gastroenteritis* (by a bacteria *Campylobacter*), cervicitis, sexually transmitted infection (STI), e.g.,Chancroid (by Chlamydia sp.), *Clostridioidesdifficile* Infection (by the spore-forming bacterium Clostridioidesdifficile),chronic obstructive pulmonary disease, i.e. COPD, in acute cystic fibrosis, dental abscess,gonococcal Infection,Granuloma Inguinale (by a bacteria Klebsiellagranulomatis, formerly known as Calymmatobacteriumgranulomatis), Legionella

Pneumonia,Lyme Disease (by bacteria the Borrelia sp., tuberculosis, ,Mycoplasma Pneumonia, Ocular Rosacea, Otitis Media (inflammatory diseases of the middle ear.), pelvic Inflammatory diseases, pharyngitis pneumonia, rheumatic fever prophylaxis, sinusitis , skin and structure Infection , STD prophylaxis, tonsillitis/pharyngitis,streptococcal infection, in early stage ofsyphilis, and in typhoid fever.

Currently Erythromycin, Clarithromycin, Azithromycin, and Fidaxomicin are worldwide used macrolide antibiotics by the medical practioners. Other macrolide antibiotics which are commonly used in different part of the world are*Carbomycin A, Josamycin, Kitasamycin,Oleandomycin,Solithromycin, Spiramycin* (it is used and approved mainly in the European Unions), *Troleandomycin* (used mostly in Italy and Turkey), *Tylosin/tylocine* (used for animals) and *Roxithromycin*.Ketolides a class of antibiotics which structure is similar to other macrolides, e.g.,*Telithromycin* (the first and only approved ketolides) and *Cethromycin* have been used to treat infections of respiratory tracts caused by macrolide-resistant bacteria. Ketolides are more effective as compared to first generation of macrolides because they possess two ribosomal binding sites.*Solithromycin*is a *Fluoroketolides,* having similar structurelike the ketolideswith a Fluorine atom in macrocylic lactone ring and possess three ribosomal interaction sites in bacteria. Apart from their the most common use in infectious diseases, macrolides antibiotics have also been used for patients suffering from cancer, auto-immune diorders, inflammations; as immunomodulaory, antifungal, antiparasitic, antimalarial and antiviralagents. [1-4]

Erythromycin the first natural macrolide was discovered in 1949 from a bacterial strain of *Streptomyces erythreus*, and was first used in asan antibiotics 1952 in the treatment of different types of bacterial infections. It was also widely used for the treatments of infection where pencillins was found to be ineffective due to penicillin-resistant bacterial strains or patients are allergic to penicillins.Due to poor stability in acidic medium and adverse-effects in gastrointestinaltracts in a significant population by the use of Erythromycin, scientists have been developed in early 1980s, the first generation semisynthetic macrolidese,g., *Clarithromycin and Azithromycin* by chemical modification in *Erythromycin. T*hese antibiotics are quite stable in acidic medium, they are easily absorb in guts and shows fewer side-effects as compared to *Erythromycin.*

Usually macrolides antibiotics are administered orally, but parenterally can also be given. The most common side effects of macrolides include abdominal discomforts as well as nausea, vomiting, diarrhea, and ringing or buzzing in the ears (tinnitus).While the more severe adverse effects are manifested in forms allergy,inflammation and congestion of bile ducts in the liver. The later one adverse effect is generally found only with the use of *Erythromycin*. Macrolides may also interact with other antibiotics if taken in combination, which may lead to

harmful effects on the heart.Colchicine toxicity symptomsare gastrointestinal discomforts, fever, myalgia, pancytopenia, and organ failure; may happen when macrolides are taken with the colchicine so macrolide are prohibited to take with it. [5-9]

Antimicrobial activities of *Erythromycin, Clarithromycin, Azithromycin, Fidaxomicin and Telithromycin*have been found to be almost similar against many pathogenic bacterialike Streptococci, Staphylococci, Clostridia, Listeria, Haemophilus sp., moxicella, and Neisseria etc. The first generation's macrolides are more effective against many gram negative bacteria as well as *Mycoplasma pneumonia, Helicobacter pylori, Cryptosporidia* and several other atypical mycobacteria as compared to *Erythromycin*. *Fidaxomicin*a bactericidal antibiotics, effective selectively against gram positive bacteria Clostridia is poorly absorbed in blood when taken orally and is used to treat *Clostridium difficile* associated diarrhea. The basic mechanism and mode of action of macrolides antibiotics involve inhibition of bacterial proteins biosynthesis by binding reversibly to the P site on the 50S sub unit ribosomes of bacteria and by preventing the activity of enzyme peptidyltransferase which facilitate the addition of amino acid by growing proteins chain attached to transfer RNA with the next amino acid. It also inhibitstranslation of bacterial ribosomal. Macrolides also shows their antimicrobial activity by premature breaking of the peptidyl-transfer RNA from the ribosome. They are mostly present within leukocytes, hence easily transported at the site of infection. [10-14]

The antibacterial spectrum activities of the most potent macrolides are comparable to β-lactam antibiotics viz. penicillin.The macrolides belong to groups of natural product compounds which are a large macrocyclic lactone ring and to which one or more deoxy sugars, viz. Cladinose and Desosamine are joined. [15-18]

The structures of macrolides

The structures basic macrolides and their ketolides derivatives contains five common chemical features (1) a macrocyclic lactone ring, comprising a 14 to 16 membered ring, (b) a multiple ketone group (C=O) & hydroxyl group (-OH), (c) a neutral sugar moiety joined either to a amine sugar residues or directly to nucleus, (d) on or two amino-sugar which are linked to nucleus lactone with glycosidic linkage and (e) a dimethyl amino residues on the sugar which impart the basicity to macrolides.[19-24]

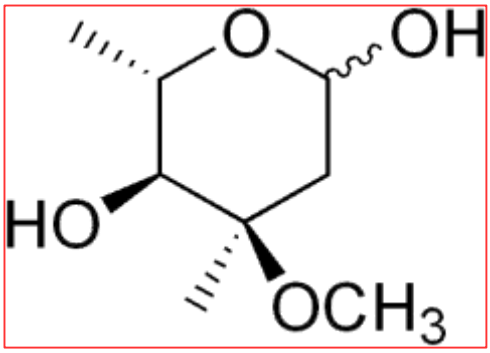


Figure (1a) Cladinose

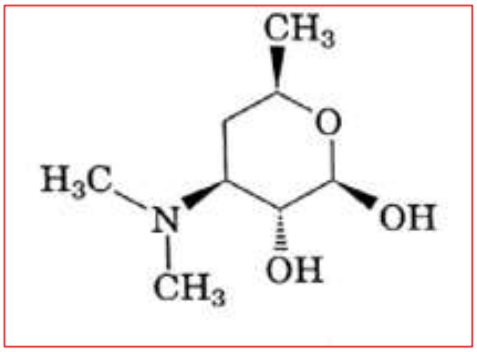


Figure (1b) Desosamine

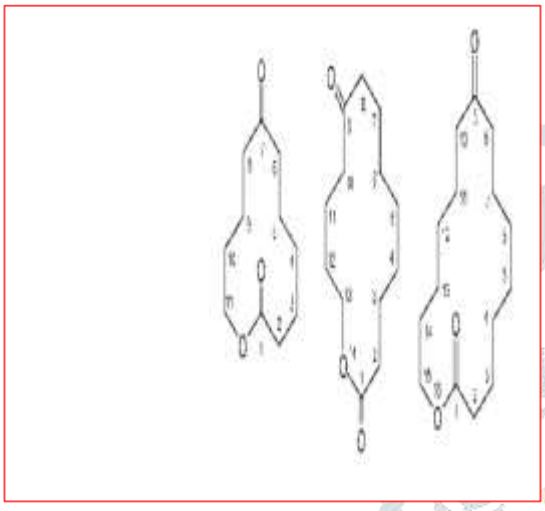
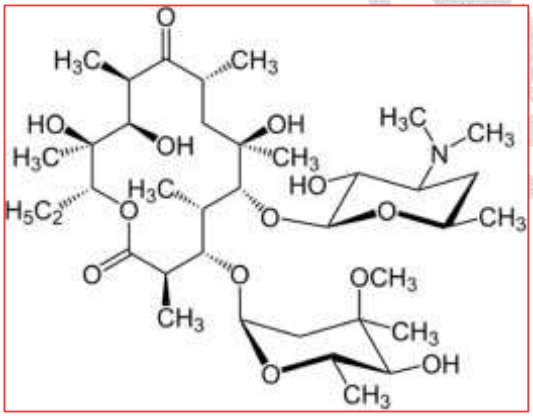
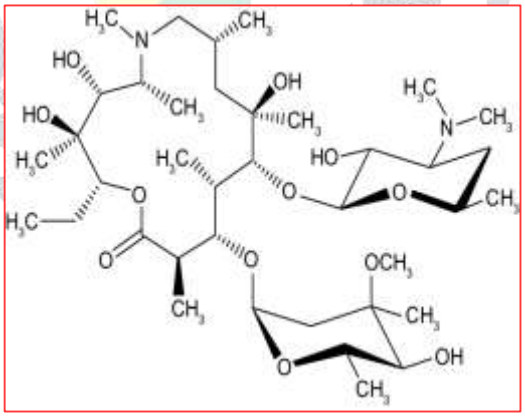


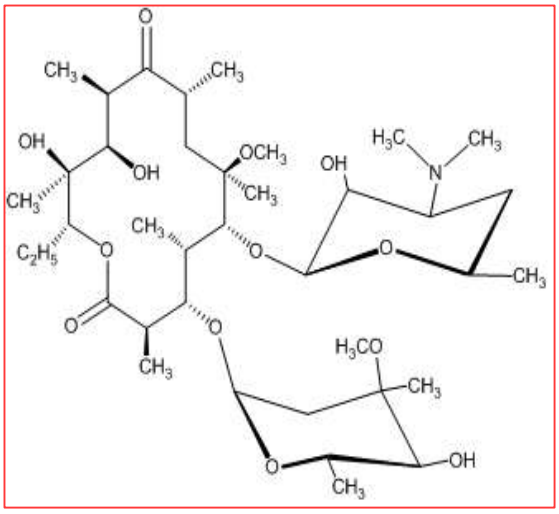
Figure (1c) Macrocyclic ring in macrolide antibiotics



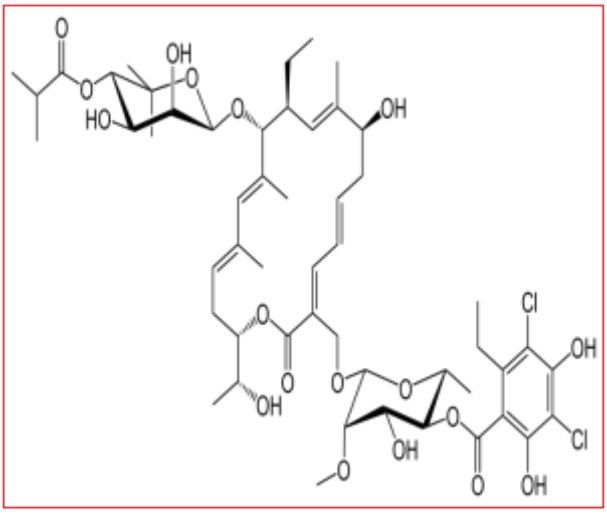
Erythromycin(1d)



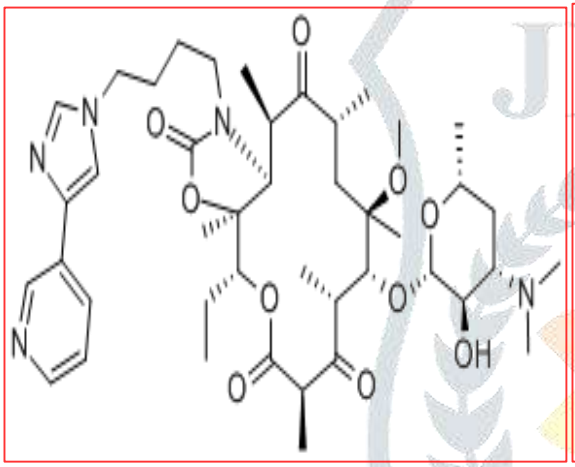
(1e) Azithromycin



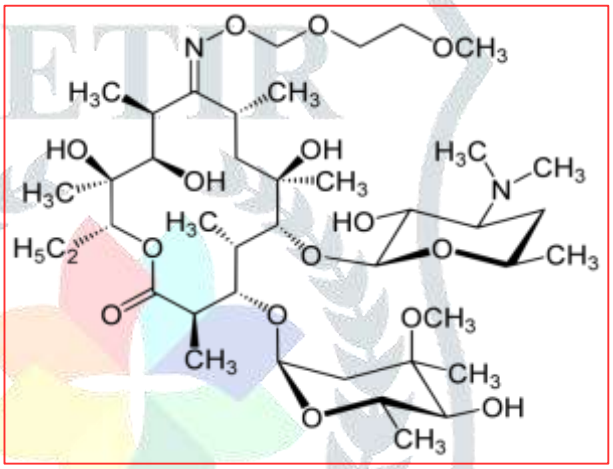
Clarithromycin (1f)



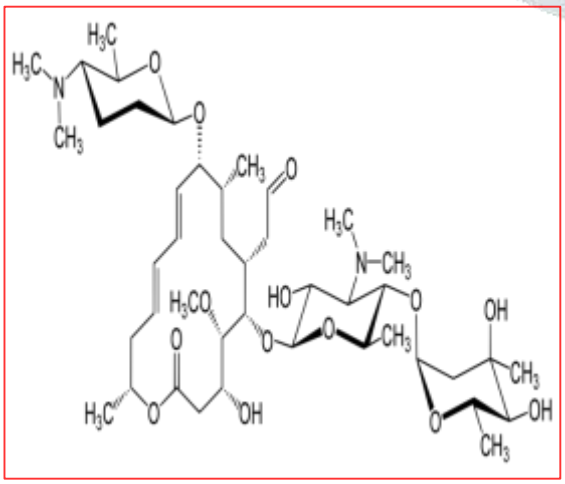
Fidaxomicin(1g)



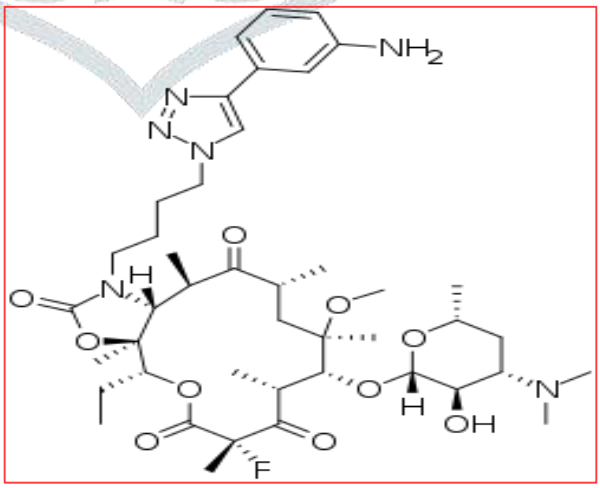
Telithromycin(1h)



Roxithromycin(1i)



Spiramycin (1j)



Solithromycin(1k)

Erythromycin is a 14-membered ring macrolide and its ring was expanded synthetically by an introduction of nitrogen which forms the 15-membered macrolide, *Azithromycin*. *Clarithromycin and Roxithromycin* are a 14-membered macrocyclic ring, whereas the large family of 16-membered macrolide antibiotics e.g. Tylosin is generally used in veterinary practice.

Mechanism of action and pharmacokinetics of Macrolidies

The most common mechanism of action macrolide antibiotics is due to the inhibition/retardation ofbiosynthesis bacterial of protein which is taking place at 50S subunits of ribosomes and macrolides antibiotic target the bacterial 50S subunit of bacterial ribosomes. Generally, in lower dose, it is bacteriostatic in action but at higher dose macrolides act as bactericidal. Structurally, bacterial ribosomes are 70Sribosomes which is further divided into two subunits (on the basis of sedimentation during centrifugation process), subunits 30S and 50S, each of which is composed of ribosomal RNA (r-RNA) and proteins. The enzyme peptidestransferase center is present at the 50S subunit of ribosomes, which catalyze the formation of new peptide bonds by joining new amino acids to the growing polypeptide chain during the biosynthesis of new proteins. Macrolide antibiotics bind to the 23S subsites of rRNA of the bacterial 50S ribosomal subunit, stop bacterial protein synthesis by decatalyzingthe activity trans-peptidase andby virtue of this,transpeptidation/translocation steps of protein synthesis is not happening. It has also been found that the bacterial ribosome interacts differently, with the macrolides during the process of translation, and the whole conformations of ribosome-macrolide complexes are regularly changing during different stages of protein biosynthesis. A rotated structure is formed during the rotations of the subunit which induce conformational change by the elongation in one dimension. Antibiotics, which interfere with ribosomal dynamics and mobility, can also lead to miscoding resultin the decrease in the protein translation rate.So many antibiotics, including the macrolides bind with 23S ribosomal RNA (rRNA)which is nearly 8–10 Å far away from the peptidyltransferasesites of the 50S subunits and from this pocket the nascent peptide exit from a tunnel.But removal of this newly formed peptide is attenuated due to close proximity occurred in the conformations of the ribosomes which are happened due to macrolides ribosome complex formation in bacterial cell.

Differences in structures of different macrolides analogs haveshown prominent influence on the binding with the 50S subunits of ribosomes and their mode of inhibition during proteins synthesis. Therefore, a lot of efforts have been made in development newer analogs with improved antibacterial activities which possess better profile as compared to first generation macrolides resistant pathogens.

Absorption of macrolide in the intestine is limited due to presence of P-glycoprotein which is encoded by the gene. This gene accelerates the excretion of macrolides into the bile. Since macrolides are lipophilic hence they are widely distributed in blood and tissues. In the bloodstream; preferentially, they bind with the binding protein alpha-1-acid glycoprotein (AGP) e.g. *Erythromycin* is 70-80% bound to AGP in the plasma However, *Azithromycin* is 93% unbound in the plasma, but only 16% unbound in liver tissue.After their absorption,they are actively concentrated within phagocytes and soeasily reach at the site of infection.Concentrations in phagocytes of *Clarithromycin* and *Azithromycin* are 400 times and 800 times as compared to their concentration in the serum. The concentrations of macrolide are 50 times greater in body tissues as compared to in the plasma. So they are easily diffused into the liver, lungs, spleen, kidneys, the breast milk and peritoneal fluids. The mechanism of action of *Fidaxomicin* is not related to *Erythromycin*.[25-32]

Mechanism of Resistance of Macrolides.

Bacterial resistance to macrolides antibiotics have been found due to following three different mechanisms (i) Alteration or Mutation in binding site of enzyme which is mediated by antibiotics. The identities of different amino acids and polynucleotides in the binding pocket completely determine the binding of macrolides with the bacterial ribosomes and mutation in this binding pocket is responsible for resistance to the antibiotics by the different strains of bacteria. The changes in enzyme due to mutation alter the target site of ribosomes which reduces the binding of macrolide. It is also reported that mutations mediated by genes,bythe post-transcriptional methylationof 23S rRNA, in which one or two methyl groups are addedto the exocyclic amino group located in 23S rRNA causescrossresistance in the macrolides analog, viz. lincosamides, and streptogramins (an MLS-resistant phenotype) with the pathogen. The other two are acquired resistance viz,(ii) the enzymes such as esterase's/phosphotransferases/glycosyltransferases/formylreductasesalso detoxify the drug encoded in plasmids of both gram-negative and gram-positive bacteria leads to resistant. (iii) The formation of ATP-mediated efflux proteins which transport the macrolide drugs outside of the cell develops resistance to drug. [33-36]

Erythromycin a bacteriostatic antibiotic first used in 1952was the first macrolide to be discovered from a strain of *Saccharopolysporaerythraea*. Erythromycin is primarily mixtures of four structurally related compounds known as erythromycins A, B, C, and D and there concentration varies. The antibacterial activity of Erythromycin A is more as compared to erythromycin B whereas the antimicrobial activity of Erythromycins C and D are nearly half the respect to erythromycin A. (Figure,1d, 2)

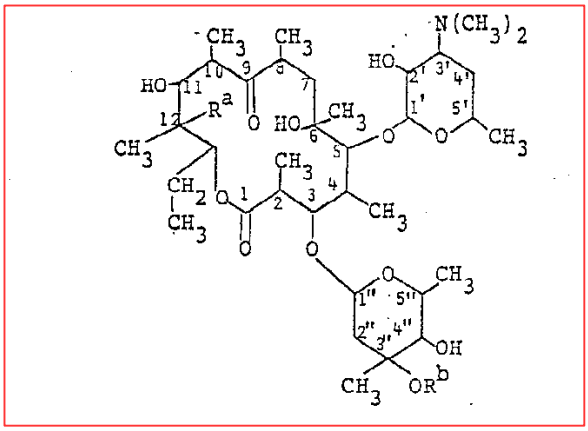


Figure 2.The subtituents in Erythromycin

After the discovery of erythromycin, many attempts have been made by the synthetic chemists to synthetized it in the laboratory. Since, it contains 10 stereo genic carbons and also many crucial points of specific substitution, so the total synthesis of erythromycin A was a formidable task. Woodward had successfully completed the synthesis of erythromycin A. The different substituents of erythromycin are given in table 1.

S.N	R^a substituents	R^b substituents
ErythromycinA	Hydroxyl	Methyl
ErythromycinB	Hydrogen	Methyl
ErythromycinC	Hydroxyl	Hydrogen
ErythromycinD	Hydrogen	Hydrogen

It is effective against bacterial infections of the skin and upper respiratory tract, infected by *Streptococcus*, *Staphylococcus*, *Haemophilus* and *Corynebacterium* genera.

It was routinely utilized as a penicillin alternative in those patients who are allergic to penicillin or have penicillin-resistant infections. It is administered in various forms e.g., intravenously, topically, and as eye drops formulations. In infants, if it is administered systemically then there is risk of Infantile Hypertrophic Pyloric Stenosis (IHPS) with the maximum risk in the first two weeks of age of infant. It is absorbed readily when orally administered. It is unstable in low pH environments and changes into metabolites. It is widely distributed in most of the body fluids, get accumulated in leucocytes and also in inflammatory liquid. It is sparsely found in spinal fluid but the rate of

diffusionincrease during meningitis through the blood-brain barrier as per dose increases. It also crosses placenta. It is mainly get concentrated into the liver; excreted from bile and by the urine (nearly 5%). The half-life elimination of oral *Erythromycin* is 2-3 hours. It is partially metabolized by an enzyme CYP3A4 to *N-desmethylerythromycin* in liver and one of the metabolites viz. 8, 9-anhydro-6, 9-hemiketal intermediate, is an agonist of motilin-receptor which increases the peristalsis causing abdominal discomforts.

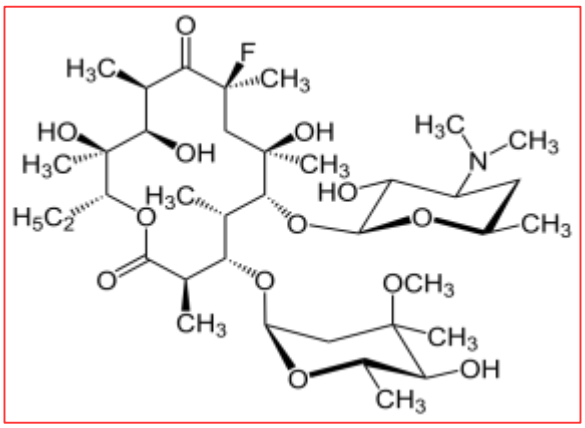


Figure 3. Structure of Flurithromycin

Flurithromycin is a fluorinated derivative of Erythtromycin A. [37-45]

Semisynthetic derivative of Erythromycin.

Since Erythromycin is less stable in acidic environment due to intramolcular cyclisation by the -OH group of carbon atoms 6,12 of macrocyclic lactone with carbonyl of 9,12 carbon atom forming a 6,9; 9,12- sprioketal. So, many semisynthetic analogs of Erythromycin have been developed which restrict the intramolecular cyclization by following strategy (a) the carbonyl group of Erythromycin has been changed with that functional groups which inhibits the ketal formation and –OH group is replaced by the methyl group.

Clarithromycin, developed in 1980 is a semisynthetic macrolide antibiotic prepared from Erythromycin by methylation of 6-OH group, chemically known as 6-O-methylerythromycin. Depending on the pathogen and its concentration Clarithromycin has been found to be bacteriostatic or bactericidal in its activity. It is effective against *Haemophylus influenza*, and it is highly effective against intracellular pathogen for example Chlamydia, legionella and others as compared to Erythromycin. The structural change of clarithromycin significantly improved its stability in acidic environment and bioavailability as compared to Erythromycin; because of lesser Hemiketal intermediates are formed. So, it causes less gastrointestinal discomforts. The first metabolized product 14-OH *Clarithromycin,*is more active. It retards the activities of hepatic microsomal CYP3A4 *isoenzyme* and of P-glycoprotein, which influence an energy-dependent efflux pump of drug. It is stable in low pH environment, well-absorbed may be taken with food, and

has increased bioavailability (52 to 55%) and its elimination half-life is longer (3.3 to 4.9 hours)as compared to *Erythromycin*.It can be administered orally twice daily. It gets easily diffused into lung tissue,saliva, sputum, alveolar macrophages, neutrophils, nasal mucosa and middle ear fluid. It is metabolized in liver by enzyme CYP3A4 and is eliminated in urine nearly 30%. The common adverse effects may be diarrhea, nausea, and abdominal discomforts. Other adverse effects of this drug are Pseudomembraneous colitis, allergic reactions which may be urticarial milder skin rashes and anaphylaxis. Sometime, it may also cause decolourisation of tooth. [46-52]

Azithromycin discovered in 1980, possessingbroad-spectrum antibacterial activity,is a macrolide antibiotic. It iseffective against anaerobic, aerobic gram-positive and more effective against gram-negative bacteria viz. *H.parainfluenza, H.influenzae, Moraxella catarrhalis,etc. It i*s also found to be highly effective against atypical intracellular organisms, likes,*Legionella pneumophila*, Mycoplasma sp and *Chlamydia sp*. It is widely used in the treatment strep throat,middle ear infections, , pneumonia, traveler's diarrhea, chronic obstructive pulmonary disease by suppressing of inflammatory processes, in the treatment of STDs and certain other intestinal infections. It can also be used during pregnancy. It is not safe in children who are younger than 6 months. It is also used for malaria in combination with other drugs. It is administered orally or intravenously. It has a long half-life and penetrates more easily in tissue. The most common adverse effects are the gastrointestinal trouble, diarrhea, abdominal cramping and nausea. When it is used for prolonged or repeated periods then it may cause oral thrush, yeast infection and or other new symptoms may develop. When administered orally the bioavailability of *Azithromycin* is found to be nearly 37% and is stable in acidic conditions. It is widely distributed in tissues and uptakes of the drug are high in the lung, tonsils and prostate. Predominantly,it is metabolized in liver by the enzyme by CYP3A4, It has a longer elimination half-life is 68 hours,eliminated via biliary excretion and nearly 6% as unchanged drug of the administered dose is excreted through the urine. [53-60]

Fidaxomicin, is a narrow spectrum bactericidal, macrocyclic antibiotics has been isolated from the fermentation of *Dactylosporangium hamdenesis*. It is effective active against gram positive bacteria, especially against*Clostridium difficile*associated illness (CDI). When taken orally, it is poorly absorbed into the bloodstream.The normal physiological conditions in the colon generally decrease the chance of recurrence of *Clostridium difficile* infection. Poorly absorbed when administered by systemic route and liver injury is minimal. It is administered twice a day for a period of 10 days. [63-66]

Spiramycin isolated in 1954 from *Streptomycesambofaciens*and have been used in Europe, Canada and Mexico,is a macrolide(16-membered macrocyclic ring)antibiotic and antiparasitic drug. It was. It is mainly bacteriostatic antibiotics but exert play bactericide action on highly

sensitive strains. It is effective against grampositive cocci and rods,gram-negative bacteria e.g., *Legionellae, mycoplasmas, chlamydiae, Toxoplasma gondii,spirochetes, and Cryptosporidium species*.But,it has been ineffective against theenterobacteria, pseudomonads and pathogenic moulds. It is administered orally as well as the parentarelly. [67-70]

Roxithromycin has been derived from *Erythromycin and* structurally contain the same number of 14-carbon atom *in* lactone ring as in *Erythromycin*, but an N-oxime side chain is attached to the lactone ring. It approved for medical use in 1987 and has been is used to treat infections of respiratory tract, urinary, and infections insoft tissue. It is not available in the US; however it is used in Australia, New Zealand, in some European countries andIsrael, South Korea.It also possesses antimalarial activity. It showsminimum drug interactions with a few hormonal contraceptives, and antacids as compared to *Erythromycin* because itshows aminimum affinity for cytochrome P450.

Most common adverse effects are gastrointestinal discomforts and while less commonadverse effects include central or peripheral nervous system pains. It is very rapidly absorbed, and easily getsdiffusedinto the most of the tissues and in phagocytic cells. It is less metabolized, half-life is 12 hours; is eliminated in unchanged form into the bile and nearly 10% is excreted from the urine.[71-72]

References.

[1].Jelic, D. &Antolovic, R., Antibiotics (Basel), 2016,**5**, 29 .

[2].Omura, S., Macrolide Antibiotics, 2nd edn, Academic Press, 2002.

[3]. Klein Joi , The Pediatric Infectious Disease Journal, 1997,**16** (4), 427–31,

[4]. Leclercq, RCourvalin, P., Leclercq, R., Rice, L., Eds., In Antibiogram,USA, 2010,305–326.

[5]. Omura, S. Macrolide Antibiotics. Chemistry, Biology and Practice; Academic Press Inc., San Diego, CA, USA, 2002.

[6]. Kaufman, H.E. , Arch. Ophthalmol. 1961, 66, 609–610.

[7]. Djoki´c, S., Kobrehel, G., Lopotar, N., Kamenar, B., Nagl, A., Mrvos, D. A. J. Chem. Res., 1988, 152–153.

[8]. "Fidaxomicin". Drugs in R&D., 2012, **10** (1), 37–45.

[9]. Scheinfeld, N., Journal of Drugs in Dermatology, 2004,**3** (4), 409–13.

[10].The erythromycins. Med J Aust., 1973, 2, 192-3.

[11]. Watanabe, Y.; Morimoto, S.; Adachi, T.; Kashimura, M.; Asaka, T.. J. Antibiot. 1993, 46, 647–660.

[12].Kirst, H.A., Schoenfeld, W., Kirst, H.A., Eds., BirkhauserVerlag: Basel, Switzerland, 2002, pp. 1–12.

[13]. Amsden, G.W. Advanced-generation macrolides, Int. J. Antimicrob. Agents 2001, 18, 11–15.

[14]. Jeli´c, D., Mutak, S., Lazarevski, G. In Medicinal Chemistry in Drug Discovery, 2013, 1–16.

[15]. Petropoulos, A.D., Kouvela, E.C., Starosta, A.L., Wilson, D.N., Dinos, G.P. ,J. Mol. Biol. 2009, 385, 1179–1192.

[16]. Zhanel, G. G., Walkty, A. J. &Karlowsky, J. A. Can. J. Infect. Dis. Med. Microbiol., 2015,**26**, 305–312.

[17].Schlünzen, F., Harms, J.M., Franceschi, F., Hansen, A.S., Bartels, H., Zarivach, R., Yonath, A., Structure , 2003, 11, 329–338.

[18]. Fajdeti´c, A., Cipci´cPaljetak, H., Lazarevski, G., Hutinec, A., Alihodzi´c, S, Derek, M., Stimac, V., Andreotti, D., Sunji´c, V., Berge, J.M., et al., Bioorg. Med. Chem., 2010, 18, 6559–6568.

[19]. Bojarska-Dahlig H. Hepatotoxicity of macrolide antibiotics., J AntimicrobChemother, 1990, 25, 475-7.

[20].Carson JL, Strom BL, Duff A, Gupta A, Shaw M, Lundin FE, Das Kl. Ann Intern Med, 1993, 119 , 576-83.

[21]. Schlünzen, F., Zarivach, R., Harms, J., Bashan, A., Tocilj, A., Albrecht, R., Yonath, A., Franceschi, F., Nature, 2001, 413, 814–821.

[22]. Fajdeti´c, A., Vinter, A., Paljetak, H.C., Padovan, J., Jakopovi´c, I.P., Kapi´c, S., Alihodži´c, S., Fili´c, D., Modri´c, M., ˇ Košuti´c-Hulita, N., et al., Eur. J. Med. Chem. 2011, 46, 3388–3397.

[23]. Kapi´c, S., Cipˇci´cPaljetak, H., PalejJakopovi´c, I., Fajdeti´c, A., Ilijaš, M., Stimac, V., Brajša, K., Holmes, D.J., Berge, J., Alihodži´c, S., Bioorg. Med. Chem. 2011, 19, 7281–7298.

[24].Periti P, Mazzei T, Mini E, Novelli A. ,Drug, 1993,9, 346-64.

[25].Gaynor, M., Mankin, A.S., Curr. Top. Med. Chem. 2003, 3, 949–961.

[26]. Bulkley, D., Innis, C.A., Blaha, G., Steitz, T.A. , Proc. Natl. Acad. Sci. USA 2010, 107, 17158–17163.

[27]. Cornish, P.V., Ermolenko, D.N., Noller, H.F., Ha, T, Mol. Cell, 2008, 30, 578–588.

[28]. Ban, N., Nissen, P,Hansen, J., Moore, P.B., Steitz, T.A., Science 2000, 289, 905–920.

[29]. Harms, J., Schluenzen, F., Zarivach, R,Bashan, A., Gat, S., Agmon, I., Bartels, H., Franceschi, F., Yonath, A. , Cell, 2001, 107, 679–688.

[30]. Yonath, A. ,Annu. Rev. Biochem. 2005, 74, 649–679.

[31]. Yu, D., Zhang, C., Qin, P., Cornish, V.P., Xu, D., Sci. China Life Sci., 2014, 57, 1131–1139.

[32]. Herman, T. Drugs targeting the ribosome, Curr. Opin.Struct. Biol. 2005, 15, 335–366.

[33]. O'Connor, M., Gregory, S.T,Dahlberg, A.E. Nucleic Acids Res. 2004, 32, 5750–5756. [34]. Bailey, M.; Chettiath, T.; Mankin, A.S., Antimicrob. Agents Chemother., 2008, 52, 866–874.

[35]. Maravi´c, G. ,Curr. Drug Targets Infect. Disord. , 2004, 4, 193–202.

[36]. Leclercq, R.; Courvalin, P. ,Antimicrob. Agents Chemother., 2002, 46, 2727–2734.

[37]. Munita JM, Arias CA , Microbiology Spectrum., 2016,4, (2), 481–511.

[38] Pal S.,Tetrahedron, 2006,62 (14), 3171–3200.

[39] Workowski KA, Berman SM, Morbidity and Mortality Weekly Report (MMWR), Recommendations and Reports, 2006,55 (RR-11): 1–94.

40]. Rodnina, M.V., Wintermayer, W., Curr. Opin.Struct. Biol., 2003, 13, 334–340.

[41]. Maheshwai N., Archives of Disease in Childhood. 2007, 92, (3), 271–3.

[42]. Kibwage IO, Hoogmartens J, Roets E, Vanderhaeghe H, Verbist L, Dubost M, et al., Antimicrobial Agents and Chemotherapy, 1985,28 (5), 630-39.

[43]. GialdroniGrassi G, Alesina R, Bersani C, Ferrara A, Fietta A, Peona V., International Journal of the Mediterranean Society of Chemotherapy ,1986,5 (3): 177–84.

[44]. Woodward RB, Au-Yeung BW, Balaram P, Browne LJ, Ward DE, Au-Yeung BW, Balaram P, Browne LJ, Card PJ, Chen CH, Journal of the American Chemical Society., 1981,103 (11), 3213–3215.

[45].Weber FH, Richards RD, McCallum RW (April). The American Journal of Gastroenterology,1993, 88 (4), 485–90.

[46]. Puri, S.K.; Lassman, H.B. Roxithromycin: A pharmacokinetic review of a macrolide. J. Antimicrob. Chemother. 1987, 20, 89–100.

[47]. Greenwood D (1ed.) Oxford, Oxford University Press, 2008, p. 239.

[48]..Kirst HA,. Macrolide Antibiotics (2ed.). Basel, Birkhäuser Basel. 2012, p. 53.

[49].Gélisse P, Hillaire-Buys D, Halaili E, Jean-Pastor MJ, Vespignan H, Coubes P, Crespel A , Revue Neurologique. , 2007, 163 (11), 1096–9.

[50].Sekar VJ, Spinosa-Guzman S, De Paepe E, De Pauw M, Vangeneugden T, Lefebvre E, Hoetelmans RM ., Journal of Clinical Pharmacology. 2008, 48 (1), 60–65.

[51]. Polis MA, Piscitelli SC, Vogel S, Witebsky FG, Conville PS, Petty B, et al. Antimicrobial Agents and Chemotherapy., 1997,41 (8), 1709–14

[52]. Ferrero JL, Bopp BA, Marsh KC, Quigley SC, Johnson MJ, Anderson DJ, et al. Drug Metabolism and Disposition,1990, 18, (4), 441–6.

[53]. Greenwood, David. Antimicrobial drugs, chronicle of a twentieth century medical triumph (1. publ. ed.). Oxford: Oxford University Press, 2008, p. 239.

[54].Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. , "Clinical practice guideline adult sinusitis". Otolaryngology–Head and Neck Surgery, 2015,152..

[55]. Levert, H., B. Gressier, I. Moutard, C. Brunet, T. Dine, M. Luyckx, M. Cazin, and J. C. Cazin. . Inflammation 1998,22,191-201

[56]. Randel A., American Family Physician, 2014, 88, (5), 338–40.

57] Neff M.J. , American Family Physician. 2004, 69, (11), 2713–5.

[58]. Mori F, Pecorari L, Pantano S, Rossi ME, Pucci N, De Martino M, Novembre E International Journal of Immunopathology and Pharmacology,2014, 27, (1), 121–6.

[59]. BanićTomišić Z Kemija U Industriji: ČasopisKemičara I KemijskihInženjeraHrvatske. ,2011, 60, (12), 603–17.

[60].Hicks LA, Taylor TH, Hunkler RJ, The New England Journal of Medicine, 2013,368 (15),1461–2.

[61].Revill, P., Serradell, N., Bolós, J. , Drugs of the Future., 2006,31 ,(6), 494.

[62]. Louie, T. J., Emery, J., Krulicki, W., Byrne, B., Mah, M. Antimicrobial Agents and Chemotherapy, 2008, 53, (1), 261–3.

[63].Johnson, Stuart, Journal of Infection, 2009,58, (6).

[64].Srivastava, Aashish, Talaue, Meliza,etal., Current Opinion in Microbiology, 2011, 14 (5), 532–43.

[65]. MuhittinEftalAvci , FerhatArslan, ŞinasiÇiftçi , Ali Ekiz , Abdullah Tüten , GökhanYildirim [1], RızaMadazli J Matern Fetal Neonatal Med. 2016,29,(13),2073-6.

[66]. R Gratzl , G Sodeck, P Platzer, W Jäger, J Graf, A Pollak, T. Thalhammer., Eur J ClinMicrobiol Infect Dis, 2002 ,21,(1),12-6.

[67]. Parker CT, Mannor K. Exemplar Abstract for Streptomyces ambofaciens ,Pinnert-Sindico ,1954.

[68]. Gerhartz, W. (exec ed), Ullmann's Encyclopedia of Industrial Chemistry. 5th ed., Vol A1, Deerfield Beach, FL, VCH Publishers, 1985, p. 525.

[69]. Fischer J, Ganellin CR, Analogue-based Drug Discovery., John Wiley & Sons. 2006 , p 498.

[70]. E Bergogne-BérézinPressemedicale,s, France , 1983, 25(39), 1982-1988,12-14.

[71] B Facinelli, P E Varaldo, Journal of chemotherapy, (Florence, Italy) ,1991.

[72].A Markham, D Faulds, Drugs, 1994, 48,(2),297-326.