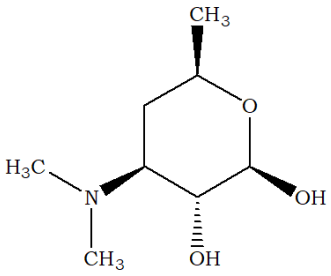
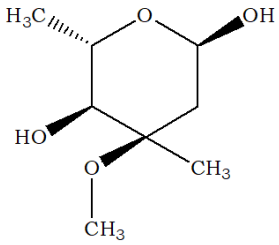
The macrolides are a major family of oral antimicrobials with established efficacy and a good tolerability profile and are thus frequently used for the treatment of community-acquired**Respiratory TractInfections** (RTIs).

- Macrolidesarebacteriostatic,meaningthatinsteadofkillingbacteria,theyrestrictorimpedetheir growth.
- The macrolides are a group of natural compounds made up of a large**macrocycliclactone** ring andone or more**deoxy sugars**, notably**cladinose** and**desosamine**.

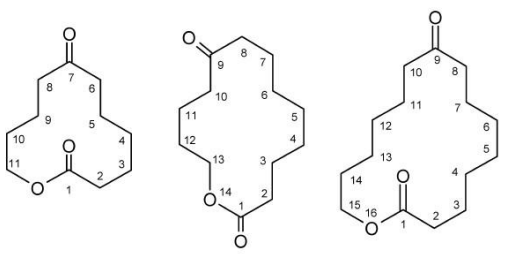


Desosamine

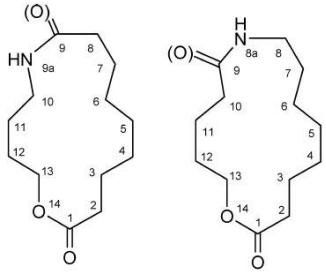


Cladinose

- Thestructuresofallmacrolides,andtheirketolide-derivatives,arebasedonamacro-lactonering,with thetherapeuticallymostrelevantmacrolidescomprisinga**14-,15-**or**16-**memberedring.
- Basicstructuresof**macrolidelactones**.

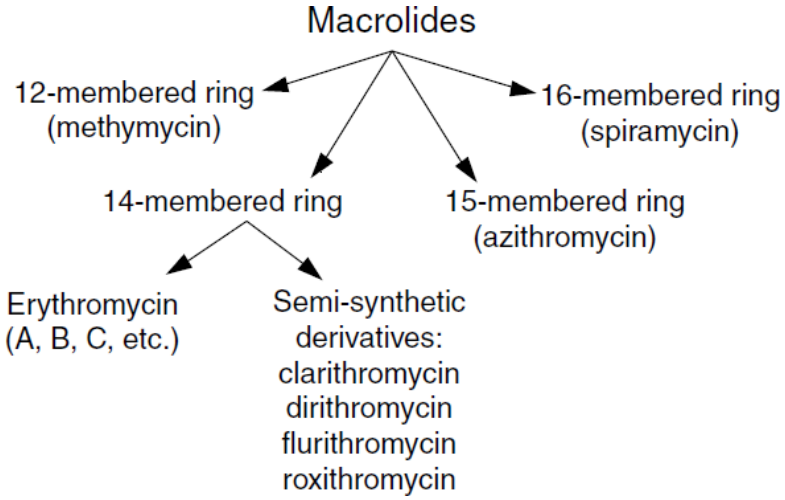


12, 14, 16-Membered lactone rings of macrolide antibiotics



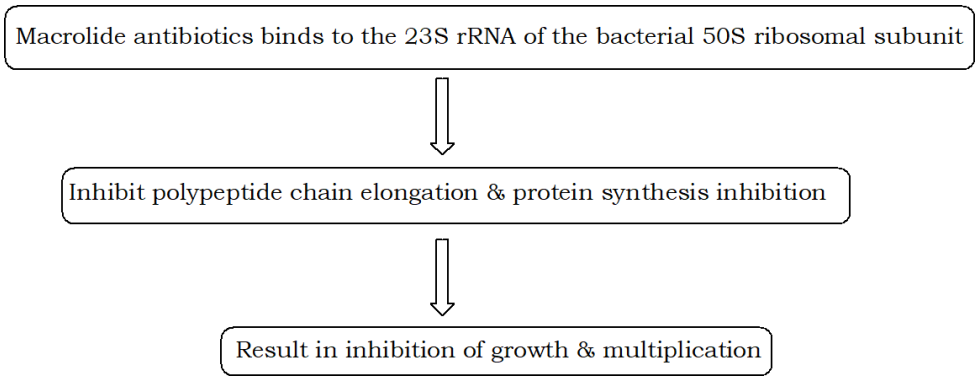
15-Membered lactone rings of 9a- and 8a-azalides or lactams

- Macrolidesstructurallycontainthreecharacteristicpartsineverymoleculelike:
  - **(i)** Amacrocycliclactoneringcontaining**14**or**16**carbonsusually.
  - **(ii)** Multipleketonegroup(**O=**)&hydroxylgroup(**-OH**).
  - **(iii)** Twodeoxysugarsattachedbyglycosidicbondwithlactonering.
- ***ClassificationAccordingtothecarbonnumberoflactonering*:**



❖ Mechanismofaction

- Macrolideantibioticsinhibitproteinsynthesisbytargetingthebacterialribosome.
- Generally,itisbacteriostaticinactionbutactsasbactericidalathigherdose.
- **Bacterialribosomes**consistoftwosubunits,**30S**and**50S**,eachofwhichiscomposedof**ribosomal RNA**(**rRNA**)and**proteins**.The**50Ssubunit**containsthe**peptidyltransferase**center,whichcatalyzes theformationofpeptidebonds,linkingaminoacidstothegrowingpolypeptidechainduringthe synthesis of new proteins.
- **Macrolideantibiotics**bindstothe**23SrRNA**ofthebacterial**50Sribosomalsubunit**.Itstops bacterialproteinsynthesisbyinhibitingthetranspeptidation/translocationstepofproteinsynthesis.
- Macrolides are actively concentrated within**leukocytes**[White blood cells (WBCs),], and thus are transported into the site of infection.



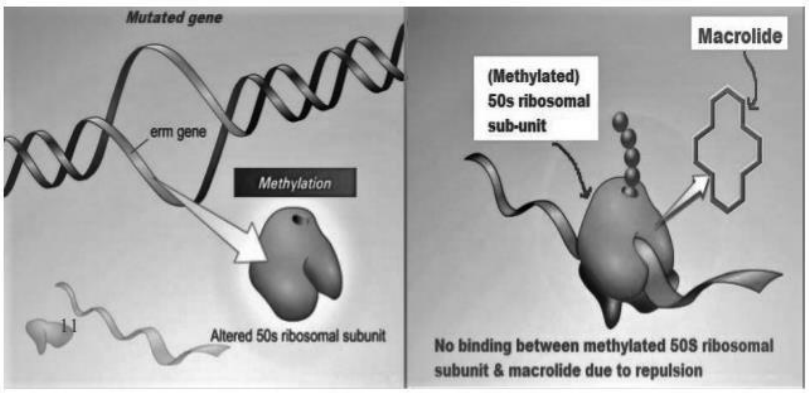
❖ MechanismofResistanceofMacrolides

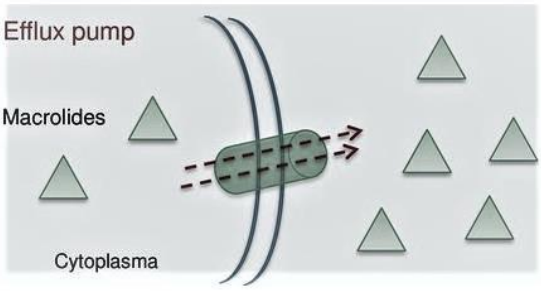
- Resistancetomacrolidesoccurbythreedifferentmechanism:

(i) ***Enzyme-mediated binding site alteration or Mutation of binding site:***Enzymatic alteration of ribosomal target reduces drug binding. Mutations in**23S rRNA**, is mediated by**erm genes**, which add one or two methyl groups to the exocyclic amino group located in**23S rRNA**.

(ii) ***Enzymatic detoxification ofthedrug***: Macrolides can be inactivated by enzymes such asesterase'sor phosphotransferases, or by glycosyltransferases, or formyl reductases encoded in plasmids of both gram-negative and gram-positive bacteria.

(iii) ***Activeefflуxofthedrug***:





Enzyme-mediated binding site alteration or Mutation of binding site

❖ TherapeuticUsesofMacrolidesAntibiotics

- Antibiotic macrolides are used to treat infections caused by Gram-positive bacteria (e.g.,*Streptococcus pneumoniae*)andlimitedGram-negativebacteria(e.g.,*Bordetellapertussis*,*Haemophilusinfluenzae*), andsomerespiratorytractandsoft-tissueinfections.
- ***MedicalConditionsAssociatedwithMacrolidesAntibiotics:***
  - ***Babesiosis***(Arare,oftensevereinfectioncausedbyprotozoaofthegenus.)
  - ***BacterialEndocarditisPrevention***(causedbythedirectinvasionofbacteria,leadingtodeformity and destruction of the valve leaflets.)
  - ***BacterialInfection***
  - ***Bartonellosis***(aninfectiousdiseaseproducedbybacteriaofthegenusBartonella.Bartonella species cause diseases such as Carrión's disease)
  - ***Bronchitis***(aninflammationoftheliningofbronchialtubes)
  - ***BullousPemphigoid***(arareskinconditionthatcauseslarge,fluid-filledblisters)
  - ***CampylobacterGastroenteritis***(atypeofgastroenteritis(gastro)causedbyabacteriaknown as *Campylobacter*)
  - ***Cervicitis***(aninflammationofthecervix,thelower,narrowendoftheuterusthatopensinto the vagina)
  - ***Chancroid***(abacterialconditionthatcausesopensoresonoraroundthegenitals.It'satypeof sexually transmitted infection [STI])
  - ***ChlamydiaInfection***(asexuallytransmittedinfection(STI)thatcanaffectanyone.)
  - ***ClostridioidesdifficileInfection***(asymptomaticinfectionduetothespore-formingbacterium *Clostridioidesdifficile*.Symptomsincludewaterydiarrhea,fever,nausea,andabdominalpain.)
  - ***ChronicObstructivePulmonaryDisease***(COPD),***Acute***
  - ***CysticFibrosis***(ageneticdisorderthataffects mostlythelungs,butalsothepancreas,liver, kidneys,andintestine.Long-termissuesincludedifficultybreathingandcoughingupmucusasa result of frequent lung infections.)
  - ***DentalAbscess***(buildupofpusthatformsinsidetheteethorgums.)
  - ***GonococcalInfection***
  - ***GranulomaInguinale***(abacterialdiseasecausedby*Klebsiellagranulomatis*,formerlyknown as*Calymmatobacteriumgranulomatis*,characterizedbygenitalulcers.)
  - ***HelicobacterPyloriInfection***
  - ***LegionellaPneumonia***(atypicalpneumoniacausedbyanyspeciesof*Legionella*bacteria)
  - ***LymeDisease***(aninfectiousdiseasecausedbythe*Borreliabacterium*)
  - ***LymphogranulomaVenereum***(isanulcerativediseaseofthegenitalarea.)
  - ***Mycobacteriumavium***(agroupofbacteriarelatedtotuberculosis.)
  - ***MycoplasmaPneumonia***(acontagiousrespiratoryinfectionthatspreadseasilythroughcontactwithrespiratoryfluids.Itcancauseepidemics.)
  - ***NongonococcalUrethritis***(aninflammationoftheurethrathatisnotcausedbygonorrheal infection.)
  - ***OcularRosacea***(inflammationthatcausesredness,burninganditchingoftheeyes.)
  - ***OtitisMedia***(inflammatorydiseasesofthemiddleear.)
  - ***PelvicInflammatoryDisease***(aninfectionofthereproductiveorgansinwomen.)

- ***Pemphigoid***(rareautoimmuneconditionsthatcausesblisteringandrashesontheskinand mucous membranes.)
- ***Pertussis***(alsoknownaswhoopingcough,isahighlycontagiousrespiratorydisease.)
- ***Pharyngitis***(inflammationofthebackofthethroat,knownasthepharynx.Ittypicallyresults in a sore throat and fever.)
- ***Pneumonia***
- ***RheumaticFeverProphylaxis***
- ***Sinusitis***
- ***SkinandStructureInfection***
- ***SkinorSoftTissueInfection***
- ***STDProphylaxis***
- ***StrepThroat***(abacterialinfectionthatcausesinflammationandpaininthethroat.)
- ***StreptococcalInfection***
- ***Syphilis(Earlystage)***
- ***Tonsillitis/Pharyngitis***
- ***Toxoplasmosis***(aninfectioncausedbyaparasite.ThisparasiteiscalledToxoplasmagondii.)
- ***TyphoidFever***
- ***UpperRespiratoryTractInfection***

❖ TheSideEffectsofMacrolidesAntibiotics

- ***Minorsideeffects:***Nausea,vomiting,diarrhea,andringingorbuzzingintheears(tinnitus).
- ***Serioussideeffects:***Includingallergicreactionandcholestatichepatitis(inflammationandcongestion of bile ducts in the liver).

❖ Interactions

- Macrolidesshouldnotbetakenwithcolchicineasitmayleadtocolchicinetoxicity.Symptomsof colchicinetoxicityincludegastrointestinalupset,fever,myalgia,pancytopenia,andorganfailure.

❖ Erythromycin

- **Erythromycin** was the first macrolide to be discovered, and it was first used in**1952**. In circumstances when patients were allergic to penicillin or had penicillin-resistant infections, erythromycin was routinely utilized as a penicillin alternative.
- Erythromycinisabacteriostaticantibioticdrugproducedbyastrainof*Saccharopolysporaerythraea* (formerly*Streptomyceserythraeus*).
- Itisavailableforadministrationinvariousforms,includingintravenous,topical,andeyedrop preparations.
- **Infants**prescribedsystemic erythromycinhadincreasedriskofIHPS[*Infantile Hypertrophic Pyloric Stenosis*(mostcommoncauseofintestinalobstructionininfancy)]withthehighestriskinthefirst2 weeks of age.

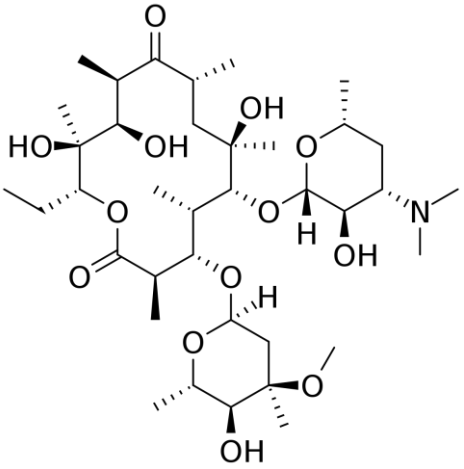
- **Pharmacokinetics:**
  - ***Absorption:***Orallyadministererderythromycinisreadilyabsorbed.Erythromycinhaspoorstability inacidicenvironmentsandisrapidlydegradedintointermediatemetabolitesafteroral administration.

  - ***Distribution:***
  - ✓ Foundinmostbodyfluidsandaccumulatesinleucocytes andinflammatoryliquid.
  - ✓ Spinalfluidconcentrationsoferythromycinarelow,however,thediffusionoferythromycinthrough theblood-brainbarrierincreasesinmeningitis,likelyduetothepresenceofinflamedtissueswhich are easily penetrated.
  - ✓ Erythromycincrossestheplacenta.

  - ***Metabolism***
  - ✓ Hepaticfirst-passmetabolismcontributessignificantlytoerythromycinmetabolismafteranoral dose.
  - ✓ ErythromycinispartiallymetabolizedbyCYP3A4enzymetoN-desmethylerythromycin.
  - ✓ Butoneofthemetabolites,**8,9-anhydro-6,9-hemiketal**intermediate,servesasa**motilin-receptor agonist**,whichisknowntoincreaseperistalsisandcausemanyofthecommonGIsideeffects.

  - ***Elimination***
  - ✓ Erythromycinconcentratesintheliverandisthenexcretedinthebile.
  - ✓ Under5%oftheorallyadministereddoseoferythromycinisfoundexcretedintheurine.
  - ✓ Theeliminationhalf-lifeoforalerythromycinwas2.4-3.1hours.

- ***UsualAdultDose***
  - **ORAL**
  - ✓ Mildtomoderateinfections:250mgorallyevery6hours,333mgorallyevery8hours,OR500mg orally every 12 hours.
  - ✓ Severeinfections:1gramorallyevery6hours.
  - ✓ Maximumdose:4grams/day.
  - **PARENTERAL**:15to 20mg/kgIVperday.



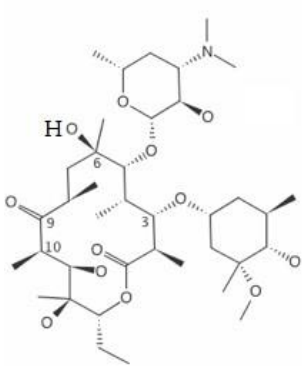
Erythromycin

❖ Clarithromycin

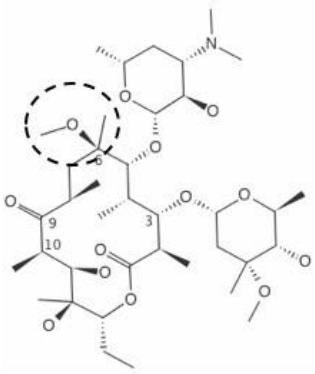
- Clarithromycinwasdevelopedin**1980**andapprovedformedicalusein**1990**.
- Clarithromycin,asemisyntheticmacrolideantibioticderivedfromerythromycinandischemically known as **6-O-methylerythromycin**.

Why does Clarithromycin Cause Less GI Side Effects than Erythromycin?

The structural configurations of clarithromycin and azithromycin provide improved acid stability as compared to erythromycin, which results in fewer hemiketal intermediates being formed and thus, less GI effects.

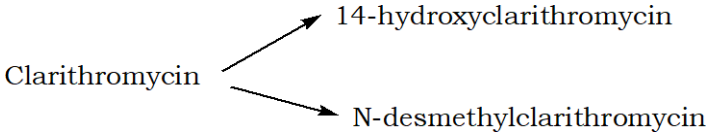


Erythromycin



Clarithromycin

- Clarithromycinmaybebacteriostaticorbactericidaldependingontheorganismanddrug concentration.
- ***Mechanismofaction***
  - Clarithromycininhibitsbacterialproteinsynthesisbybindingtothebacterial**50Sribosomal** subunit.
  - Clarithromycinisfirstmetabolizedto**14-OHclarithromycin**,whichisactiveandworks synergistically with its parent compound.
  - ClarithromycinalsoinhibitsthehepaticmicrosomalCYP3A4isoenzymeandP-glycoprotein,an energy-dependent drug efflux pump.
- **Pharmacokinetics:**
  - ***Absorption:***Clarithromycin iswell-absorbed, acid stableand maybetakenwithfood.
  - ***Distribution:***
  - ✓ The pharmacokinetic advantages that clarithromycin has over erythromycin include increased oral bioavailability(52to55%),increasedplasmaconcentrations(meanmaximumconcentrationsranged from 1.01 to 1.52 mg/L and 2.41 to 2.85 mg/L after multiple 250 and 500mg doses, respectively),and a longer elimination half-life (3.3 to 4.9 hours) to allow twice daily administration.
  - ✓ In addition, clarithromycin has extensive diffusion into saliva, sputum, lung tissue, epithelial lining fluid, alveolar macrophages, neutrophils, tonsils, nasal mucosa and middle ear fluid.
  - ***Metabolism***
  - ✓ Hepatic-predominantlymetabolizedby**CYP3A4**resulting innumerousdruginteractions.

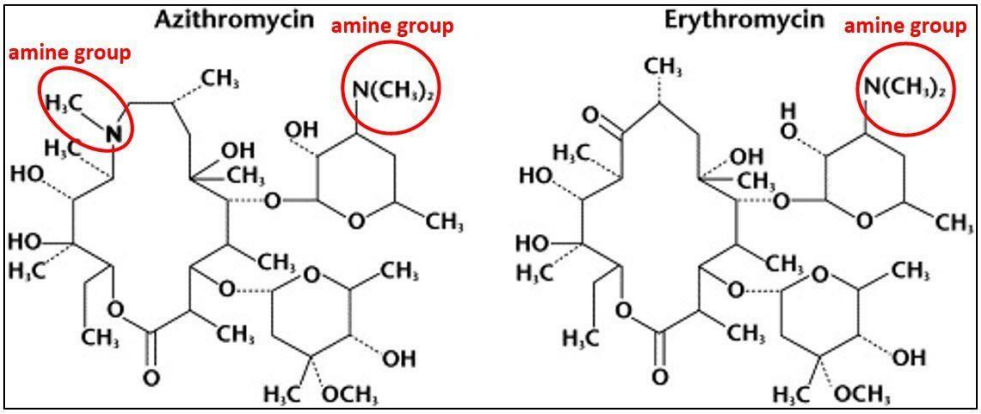


  - ***Elimination***
  - ✓ Theurinaryexcretionofclarithromycinissomewhatgreater,approximately30%.

- **Toxicity**
  - ✓ Symptoms of toxicity include diarrhea, nausea, abnormal taste, dyspepsia, and abdominaldiscomfort.
  - ✓ ***Pseudomembraneous colitis***has been reported with clarithromycin use. Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis and Stevens-Johnson syndrome have also occurred.
  - ✓ Clarithromycinmayalsocausetoothdecolourationwhichmayberemovedbydentalcleaning.
- **Dose**(***Adultdosage***)
  - ✓ Oraltablet:250mg-500mgtakenevery12hoursfor14days.
  - ✓ Extended-releaseoraltablet:1,000mgtakenevery24hoursfor14days.

❖ Azithromycin

- Azithromycinisabroad-spectrummacrolideantibioticactagainstbothanaerobicandaerobicGram- positive and Gram-negative bacteria with a long half-life and a high degree of tissue penetration.
- Azithromycinwasdiscoveredin1980andapprovedformedicalusein1988.
- InMarch2020,asmallstudywasfundedbytheFrenchgovernmenttoinvestigatethetreatmentofCOVID-19.
- Azithromycin has broad antimicrobial activity against both anaerobic and aerobic Gram-positive and Gram-negative bacteria.3 However, azithromycin may have greater activity against Gram-negative organisms, especially*Haemophilus influenzae*,*Haemophilus parainfluenza*,*Moraxella catarrhalis*, Neisseria gonorrhea, Ureaplasma urealyticum, and*Borrelia burgdorferi*. Like other macrolides azithromycin is also highly effective against atypical intracellular organisms, such as*Legionella pneumophila*, *Chlamydia spp*, and*Mycoplasma spp*.
- Azithromycinappearstobeeffectiveinthetreatmentofchronicobstructivepulmonarydiseasethrough its suppression of inflammatory processes.
- Usingazithromycinduringpregnancyhasbeenconfirmedtobesafe.



- ***Mechanismofaction***:Azithromycinbindstothe23SrRNAofthebacterial50Sribosomalsubunit.It stopsbacterialproteinsynthesisbyinhibitingthetranspeptidation/translocationstepofprotein synthesis.
- **Pharmacokinetics:**
  - ***Absorption:***Bioavailability of azithromycin is 37% following oral administration. Absorption is not affected by food. Azithromycin is an acid-stable antibiotic, so it can be taken orally with no need of protection from gastric acids.
  - ***Distribution:***
  - ✓ Afteroraladministration,azithromyciniswidelydistributedintissues.
  - ✓ Thelung,tonsilsandprostateareorganshaveshownaparticularlyhighrateofazithromycin uptake.
  - ✓ In-vivostudiesdemonstratethatconcentrationinphagocytesmaycontributetoazithromycindistribution to inflamed tissues Label.
  - ***Metabolism***
  - ✓ Hepatic-predominantlymetabolizedby**CYP3A4**.
  - ***Elimination***
  - ✓ Azithromycinispredominatelyeliminatedthroughbiliaryexcretion,andapproximately6%oftheadministere ddoseisexcretedthroughtheurineasunchangeddrug.
- **Sideeffects:**
  - ✓ Themostcommontreatmentrelatedsideeffectsinvolvethegastrointestinaltract,includingdiarrhea, nausea, and abdominal cramping.
  - ✓ Useofthismedicationforprolongedorrepeatedperiodsmayresultinoralthrushoranewyeast infectionandachangeinvaginaldischarge,orothernewsymptoms.
- **Dose:**
  - ✓ Adultdosage500mgonceperdayfor3daysandChilddosageis10mg/kgofbodyweightonceper day for 3 days.
  - ✓ Thisdrugshouldnotbeusedinchildrenwhoareyoungerthan6months.