MACROLIDE ANTIBIOTICS

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Macrolide Antibiotics

- **Biological Source:** Among the many antibiotics isolated from the actinomycetes is the group of chemically related compounds called the macrolides.
- Currently, more than 40 such compounds are known. Of all of these, only two, erythromycin and oleandomycin, have been available consistently for medical use in the United States.
- In recent years, interest has shifted away from novel macrolides isolated from soil samples (e.g., spiramycin, josamycin, and rosamicin), all of which thus far have proved to be clinically inferior to erythromycin and semisynthetic derivatives of erythromycin (e.g., clarithromycin and azithromycin), which have superior pharmacokinetic properties because of their enhanced acid stability and improved distribution properties.

Mechanism of Action

Some details of the mechanism of antibacterial action of erythromycin are known. It binds selectively to a specific site on the 50S ribosomal subunit to prevent the translocation step of bacterial protein synthesis

Spectrum of Activity

The macrolides are generally effective against most species of Gram-positive bacteria, both cocci and bacilli, and exhibit useful effectiveness against Gram-negative cocci, especially Neisseria spp.

Many of the macrolides are also effective against Treponema pallidum. In contrast to penicillin, macrolides are also effective against Mycoplasma, Chlamydia, Campylobacter, and Legionella spp.

Their activity against most species of Gram-negative bacilli is generally low and often unpredictable, though some strains of H. influenzae and Brucella spp. are sensitive.

Chemistry of Macrolide Antibiotics

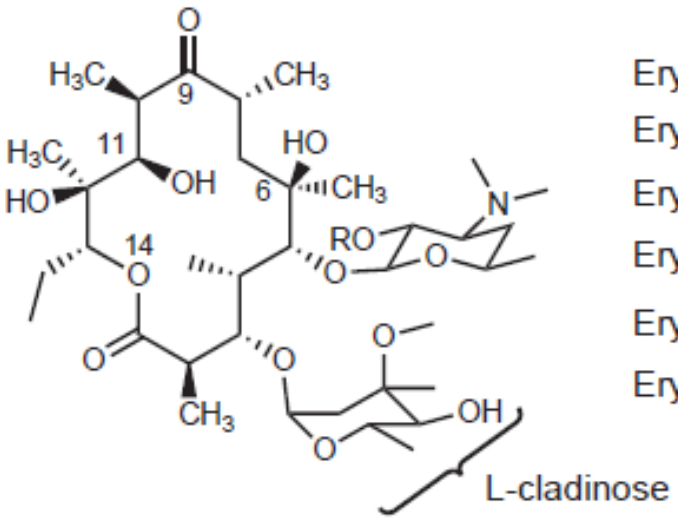
- The macrolide antibiotics have three common chemical characteristics:
- (a) a large lactone ring (which prompted the name macrolide), (b) a ketone group, and

  (c) a glycosidically linked amino sugar.

- Usually, the lactone ring has 12, 14, or 16 atoms in it, and it is often unsaturated, with an olefinic group conjugated with the ketone function.

- They may have, in addition to the amino sugar, a neutral sugar that is linked glycosidically to the lactone ring. Because of the dimethylamino group on the sugar moiety, the macrolides are bases This feature has been used to make clinically useful salts. The free bases are only slightly soluble in water but dissolve in somewhat polar organic solvents. They are stable in aqueous solutions at or below room temperature but are inactivated by acids, bases, and heat.

Problems Associated with Erythromycin



Erythromycin A

Erythromycin base

Erythromycin hydrochloride

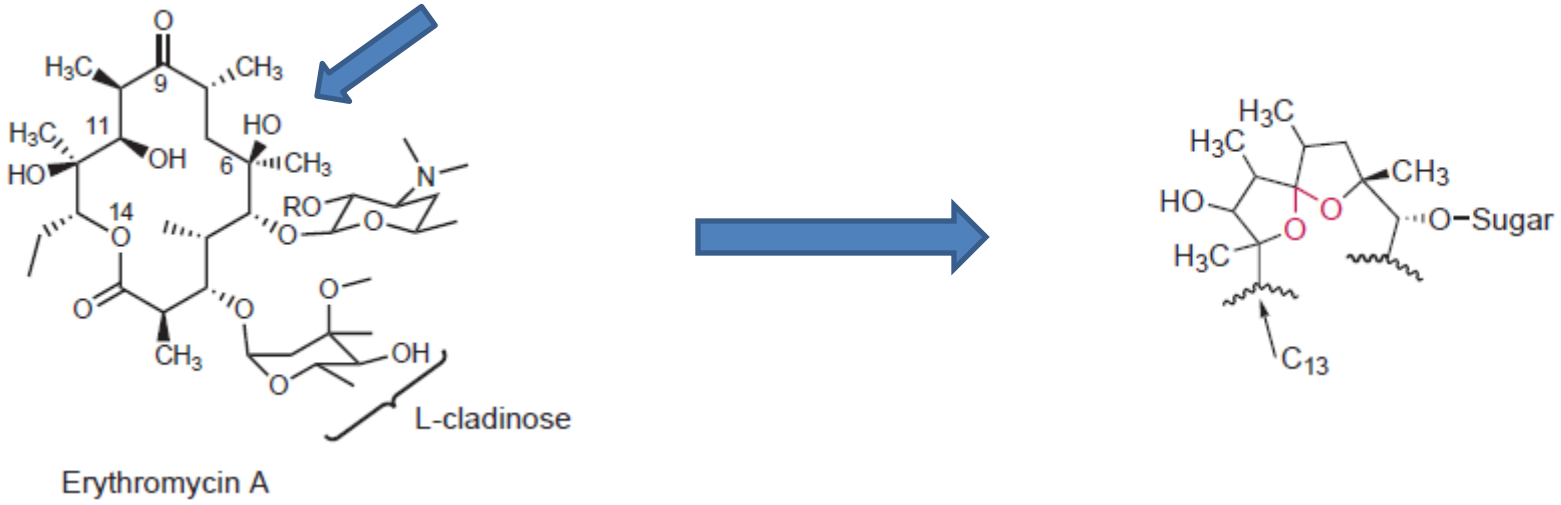
Erythromycin estolate

Erythromycin ethylsuccinate

Erythromycin lactobionate

Erythromycin stearate

The early macrolides of the erythromycin class are chemically unstable due to rapid acid-catalyzed internal cyclic ketal formation, leading to inactivity.



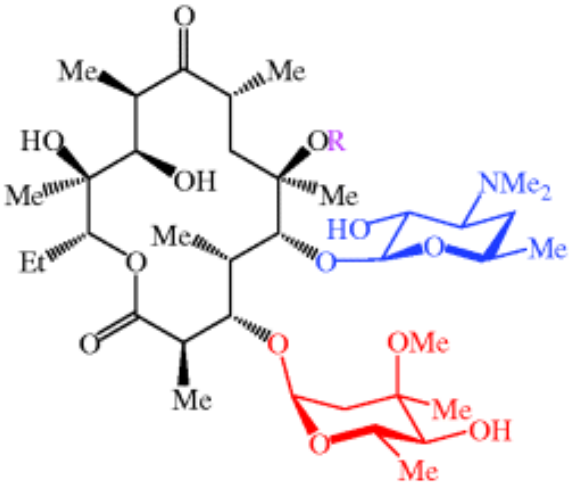
Acid-catalyzed intramolecular ketal formation with erythromycin.

The C-6 hydroxy group is involved in the process, initiated by protons, leading to internal cyclic ketal formation in erythromycin that results in drug inactivation. This ketal, or one of the products of its subsequent degradation, is also associated with GI cramping.

Clarithromycin

Clarithromycin is the 6-methyl ether of erythromycin. The simple methylation of the 6-hydroxyl group of erythromycin creates a semisynthetic derivative that fully retains the antibacterial properties of the parent antibiotic, with markedly increased acid stability and oral bioavailability and reduced GI side effects associated with erythromycin.

Evidence suggests that the hemiketal may be largely responsible for the GI (prokinetic) adverse effects associated with oral erythromycin.



Clarithromycin (R = Me)
Erythromycin (R = H)

Clarithromycin is well absorbed following oral administration. Its oral bioavailability is estimated to be 50% to 55%.

Advantage of Clarithromycin

Conversion of the molecule to its more lipophilic methyl ether prevents internal ketal formation, which not only gives better blood levels through chemical stabilization, but also results in less gastric upset.

An extensive saturable first-pass liver metabolism of clarithromycin leads to formation of its C-14 hydroxy analog, which has even greater antimicrobial potency, especially against Haemophilus influenzae.

The enhanced lipophilicity of clarithromycin also allows for lower and less frequent dosage for mild infections.

Azithromycin

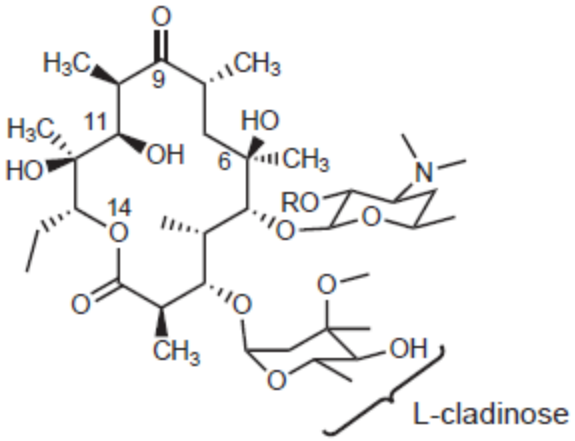
Azithromycin, called an "azalide," has been formed by semisynthetic conversion of erythromycin to a ring-expanded analog in which an N-methyl group has been inserted between carbons 9 and 10 and the carbonyl moiety is thus absent.

Azithromycin has a 15-membered lactone ring. This new functionality does not form a cyclic internal ketal.

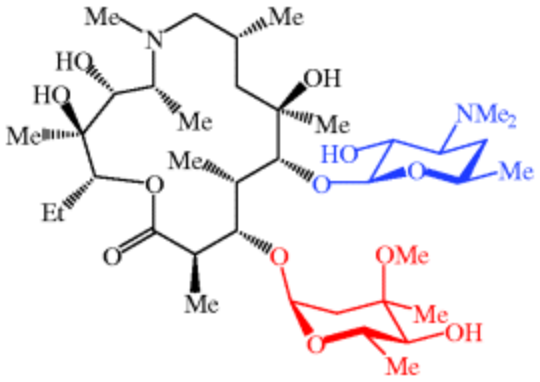
These changes also increase the lipid solubility of the molecule, thereby conferring unique pharmacokinetic and microbiological properties.

Not only is azithromycin more stable to acid degradation than erythromycin, but it also has a considerably longer half-life, attributed to greater and longer tissue penetration, allowing once-a-day dosage.

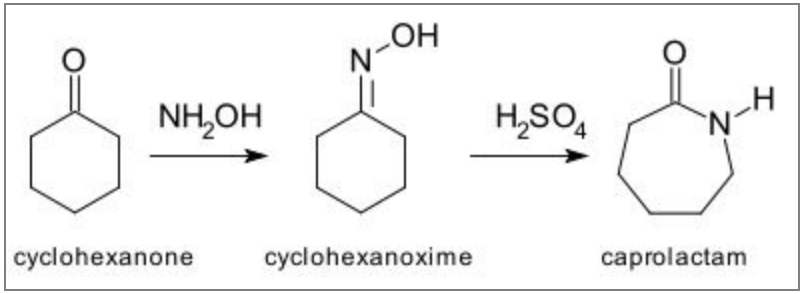
Beckmann rearrangement followed by reduction and methylation



Erythromycin A



Azithromycin



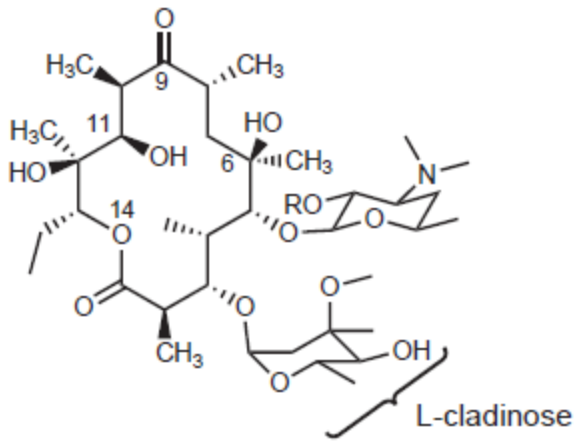
General Example of Beckmann Rearrangement for conversion of Ketone to amide

The oral bioavailability of azithromycin is good, nearly 40%, provided the antibiotic is administered at least 1 hour before or 2 hours after a meal. Food decreases its absorption by as much as 50%.

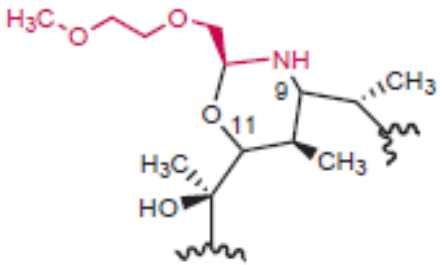
In general, it is more active against Gram-negative bacteria and less active against Gram-positive bacteria than its close relatives. The greater activity of azithromycin against H. influenzae, and M. pneumoniae and treatment of respiratory tract infections caused by these pathogens. The clinical efficacy of azithromycin in the treatment of urogenital and other sexually transmitted infections caused by Chlamydia trachomatis, N. gonorrhoeae, H. suggests that single dose therapy.

Dirithromycin

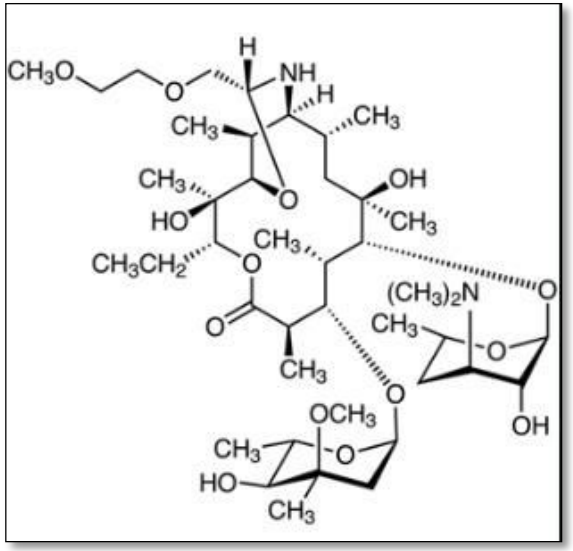
Dirithromycin is a more lipid-soluble prodrug derivative of 9S-erythromycyclamine



Erythromycin A



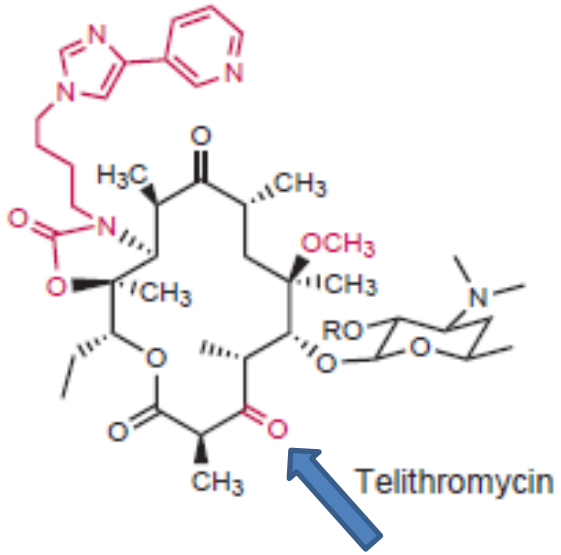
Dirithromycin



The incidence and severity of GI adverse effects associated with dirithromycin are similar to those seen with oral erythromycin.

Ketolides

The ketolides are a group of agents that are characterized by oxidation of the 3 position from an alcohol to a ketone. They are active against a significant number of erythromycin-resistant microorganisms.



Telithromycin is orally effective in the treatment of community-acquired pneumonia, chronic bronchitis, and acute sinusitis. Its principle advantage is activity against macrolide-resistant infections but significant liver toxicity has been observed.