Pharmaceutical chemistry

Antibacterial Antibiotics

Macrolides, Lincomycins,

Oxazolidinones, Polypeptides and

Unclassified antibiotics Chloramphenicol

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Macrolides

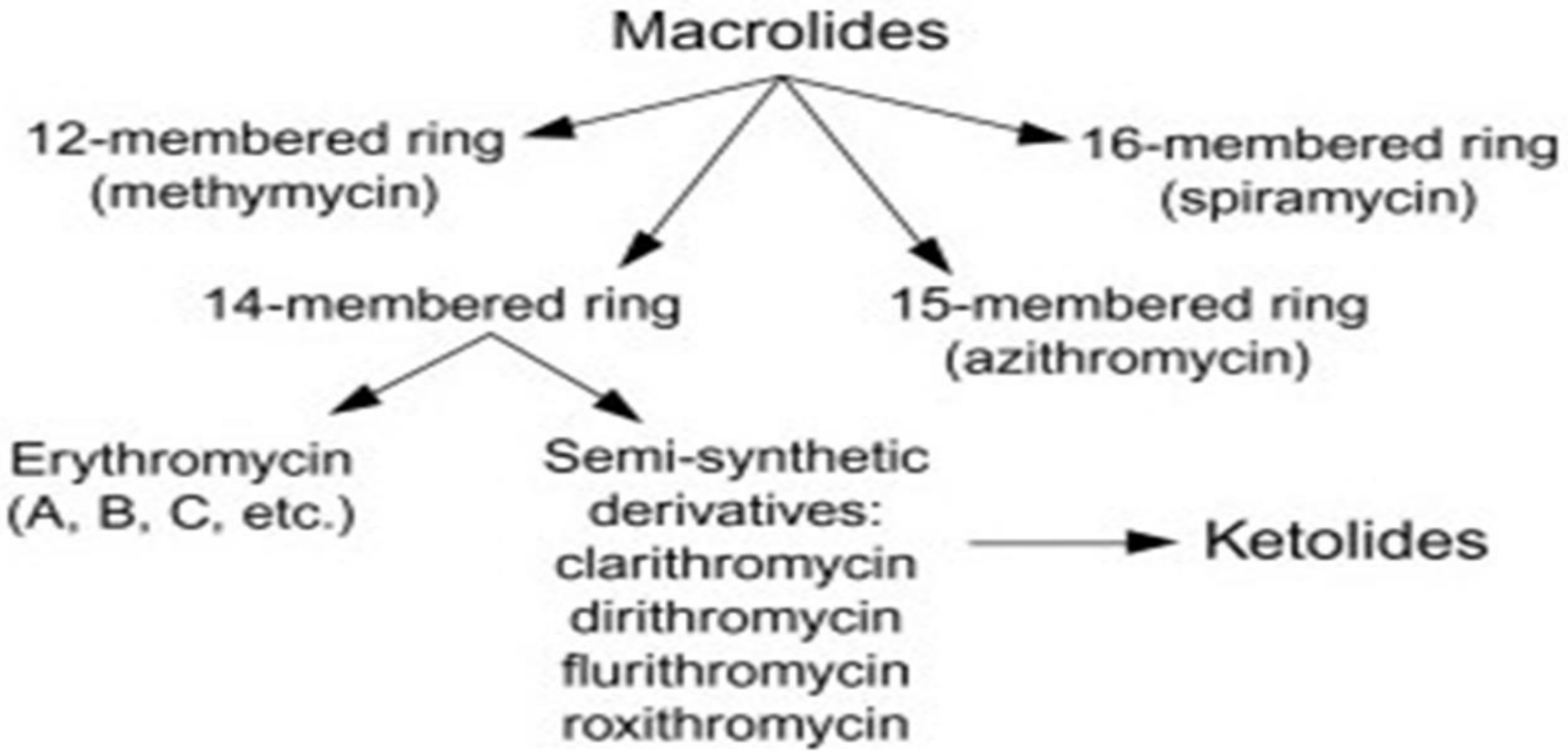
The macrolide antibiotics have three common chemical characteristics:

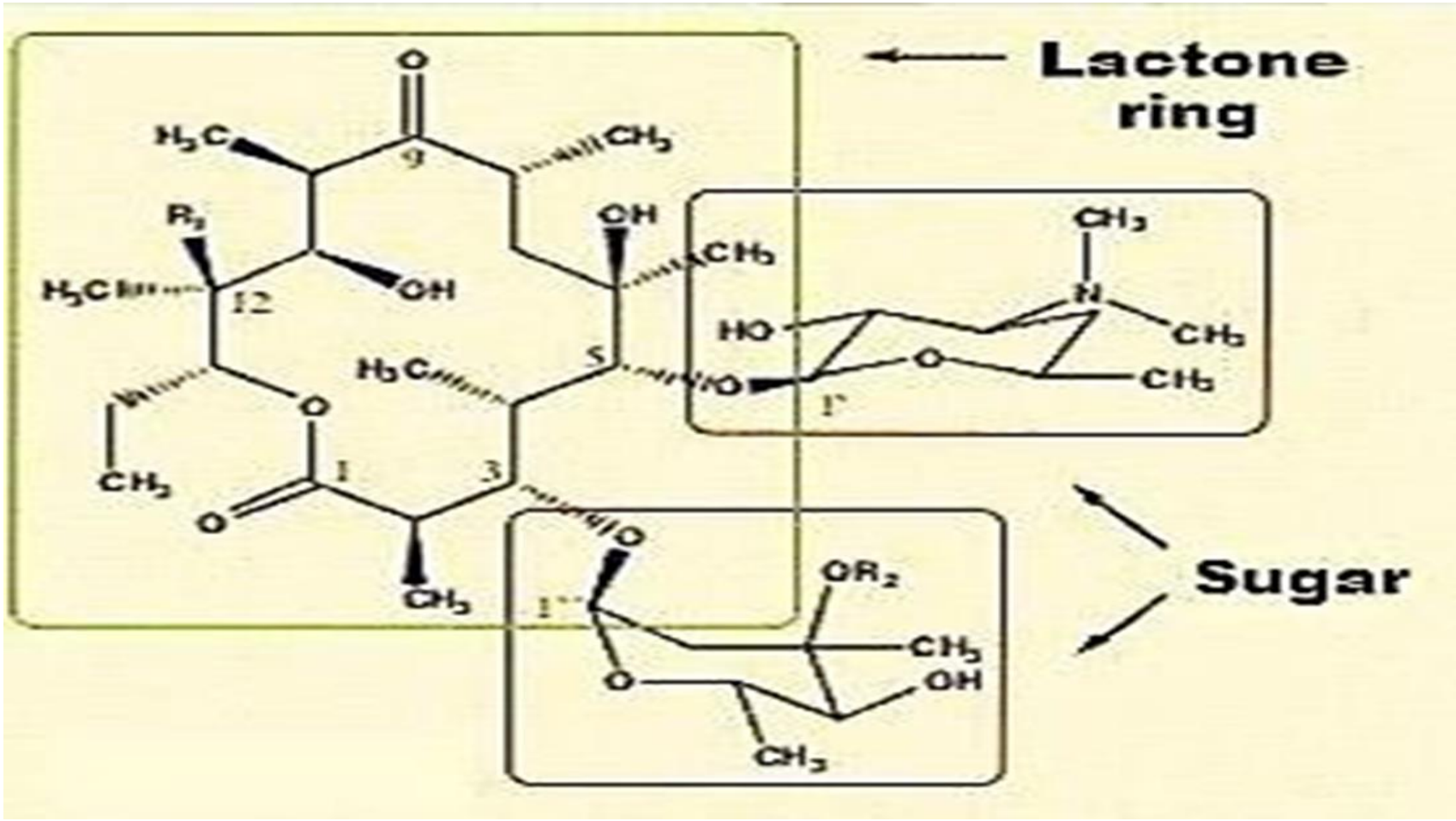
(a) a large lactone ring (which prompted the name macrolide),

(b) a ketone group

(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.


Macrolides
12-membered ring
(methymycin)
16-membered ring
(spiramycin)
14-membered ring
15-membered ring
(azithromycin)
Erythromycin
(A, B, C, etc.)
Semi-synthetic
derivatives:
clarithromycin
dirithromycin
flurithromycin
roxithromycin
Ketolides


Lactone ring
Sugar

Mechanism of Action and Resistance

It binds selectively to a specific site on the 50S ribosomal subunit to prevent the translocation step of bacterial protein synthesis.

It does not bind to mammalian ribosomes.

Broadly based, nonspecific resistance to the antibacterial action of erythromycin among many species of Gram- negative bacilli appears to be largely related to the inability of the antibiotic to penetrate the cell walls of these organisms

Spectrum of Activity

The spectrum of antibacterial activity of the more potent macrolides, such as erythromycin, resembles that of penicillin.

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.

Products

Erythromycin

The commercial product is erythromycin A,

The amino sugar attached through a glycosidic link to C- 5 is desosamine, a structure found in several other macrolide antibiotics.

The tertiary amine of desosamine (3,4,6- trideoxy-3 dimethyl amino-D-xylo-hexose) confers a basic character to erythromycin and provides the means by which acid salts may be prepared.

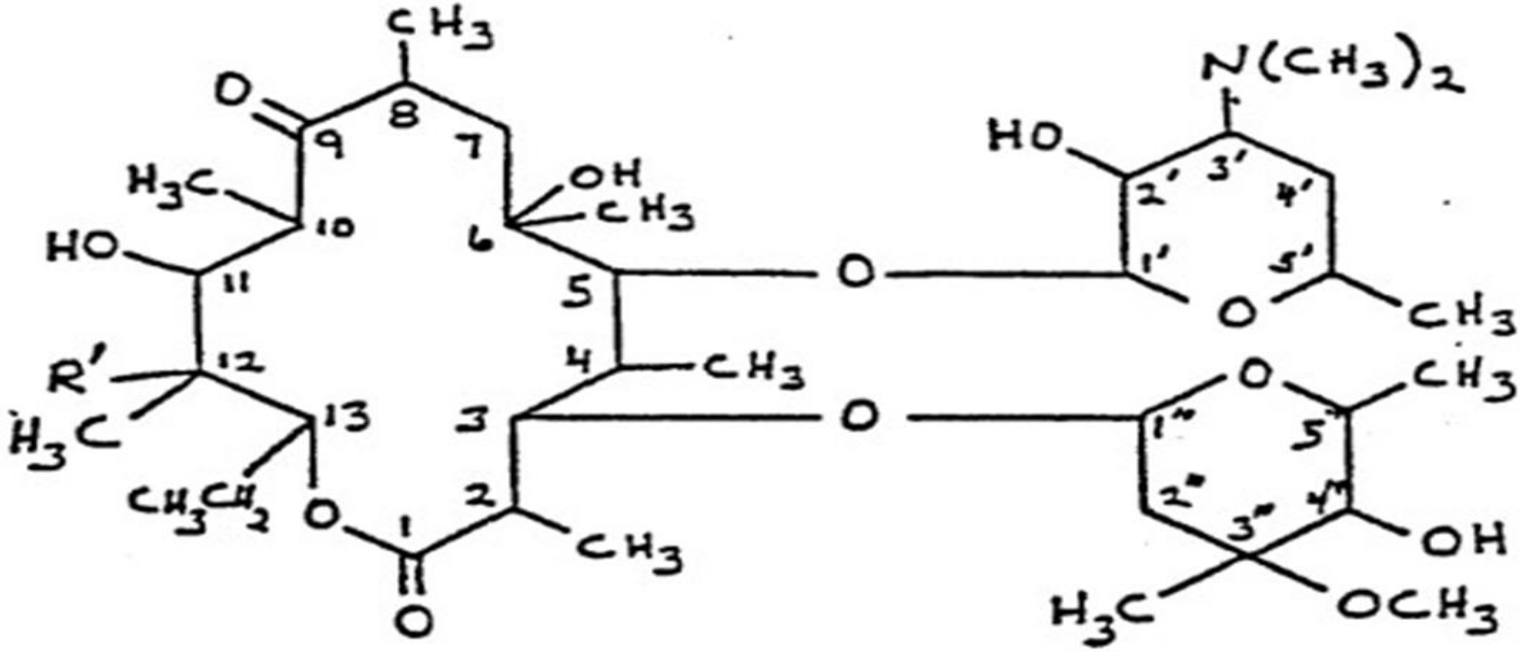
The other carbohydrate structure linked as a glycoside to C-3 is called cladinose (2,3,6- trideoxy-3-methoxy -3-C-methyl-L-ribo-hexose) and is unique to the erythromycin molecule.

Two such analogs have been found, erythromycins B and C. Erythromycin B differs from erythromycin A only at C-12, at which a hydrogen has replaced the hydroxyl group.

The B analog is more acid stable but has only about 80% of the activity of erythromycin.

The C analog differs from erythromycin by the replacement of the methoxyl group on the cladinose moiety with a hydrogen atom.

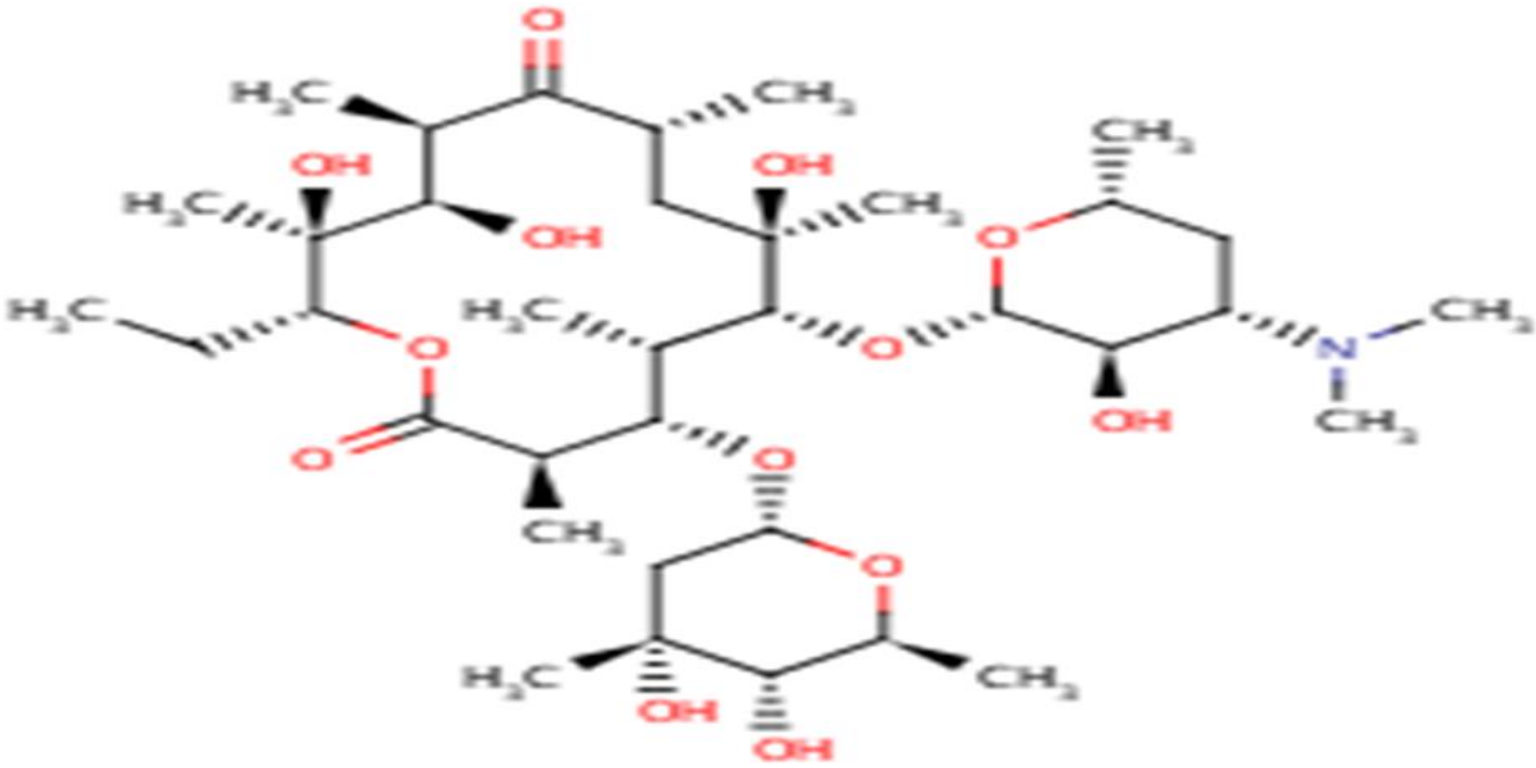
It appears to be as active as erythromycin but is present in very small amounts in fermentation liquors.



I (a) $R' = OH$; Erythromycin A

(b) $R' = H$; Erythromycin B

Erythromycin C



Erythromycin has been chemically modified with primarily two different goals in mind:

- Increase either its water or its lipid solubility for parenteral dosage forms and
- Increase its acid stability (and possibly its lipid solubility)

for improved oral absorption.

The nucleophilic functionality of 6-hydroxyl group Initiate Erythromycin degradation.

If the size of the group kept small so as not to affect the ribosomal binding.

It is extremely unstable at a pH of 4 or below. The optimum pH for stability of erythromycin is at or near neutrality.

Erythromycin is unstable to stomach acids, but can be taken orally in a tablet form

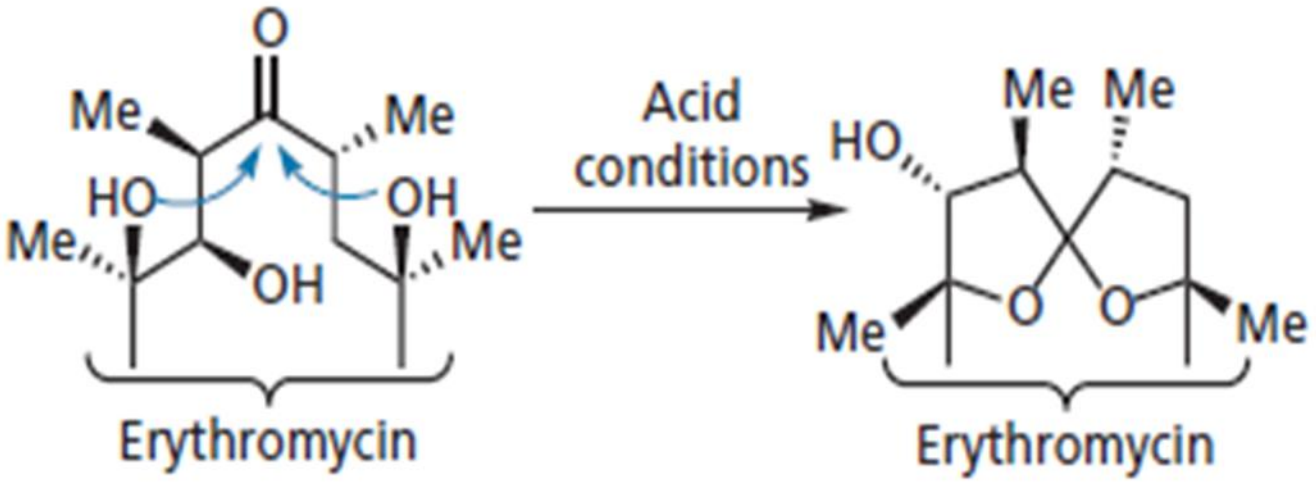
The formulation of the tablet involves a coating that is designed to protect the tablet during its passage through the stomach, but which is soluble once it reaches the intestines (enterosoluble).

The acid sensitivity of erythromycin is due to the presence of a ketone and two alcohol groups which are set up for the acid- catalysed intramolecular formation of a ketal. One way of preventing this is to protect the hydroxyl groups.

For example,

Clarithromycin is a methoxy analogue of erythromycin which is more stable to gastric juices and has improved oral absorption.

Another method of increasing acid stability is to increase the size of the macrocycle to a 16-membered ring.



Intramolecular ketal formation in erythromycin

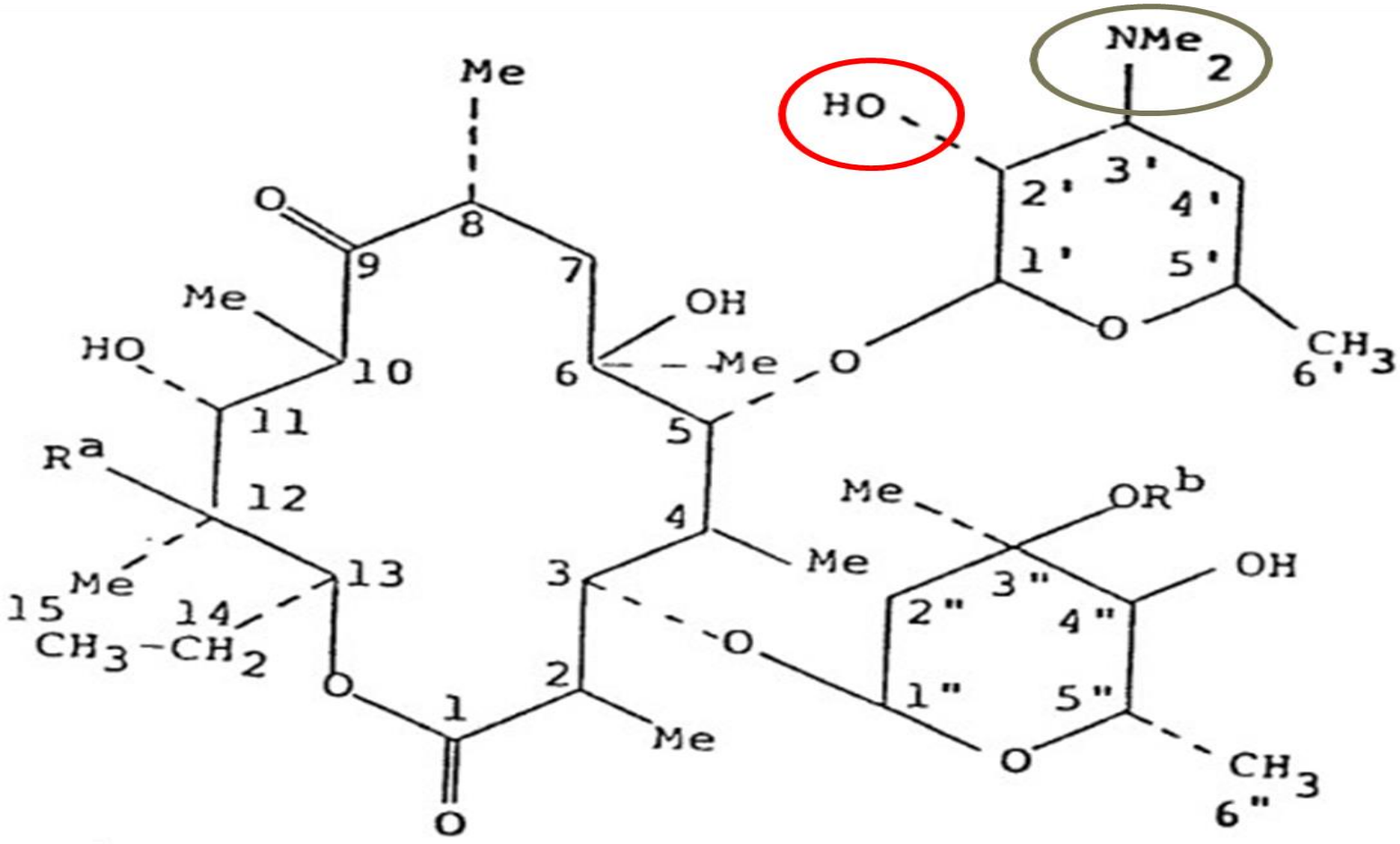
Modified derivatives of the antibiotic are of two types:

1.Acid salts of the dimethyl amino group of the desosamine moiety (e.g., the glucoheptonate, the lactobionate, and the stearate)

2.Esters of the 2`-hydroxyl group of the desosamine (e.g., the ethylsuccinate and the propionate, available as the lauryl sulfate salt and known as the estolate).

The stearate salt and the ethylsuccinate and propionate esters are used in oral dose forms intended to improve absorption of the antibiotic.

The stearate releases erythromycin base in the intestinal tract, which is then absorbed.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CH3-CH2
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CH3
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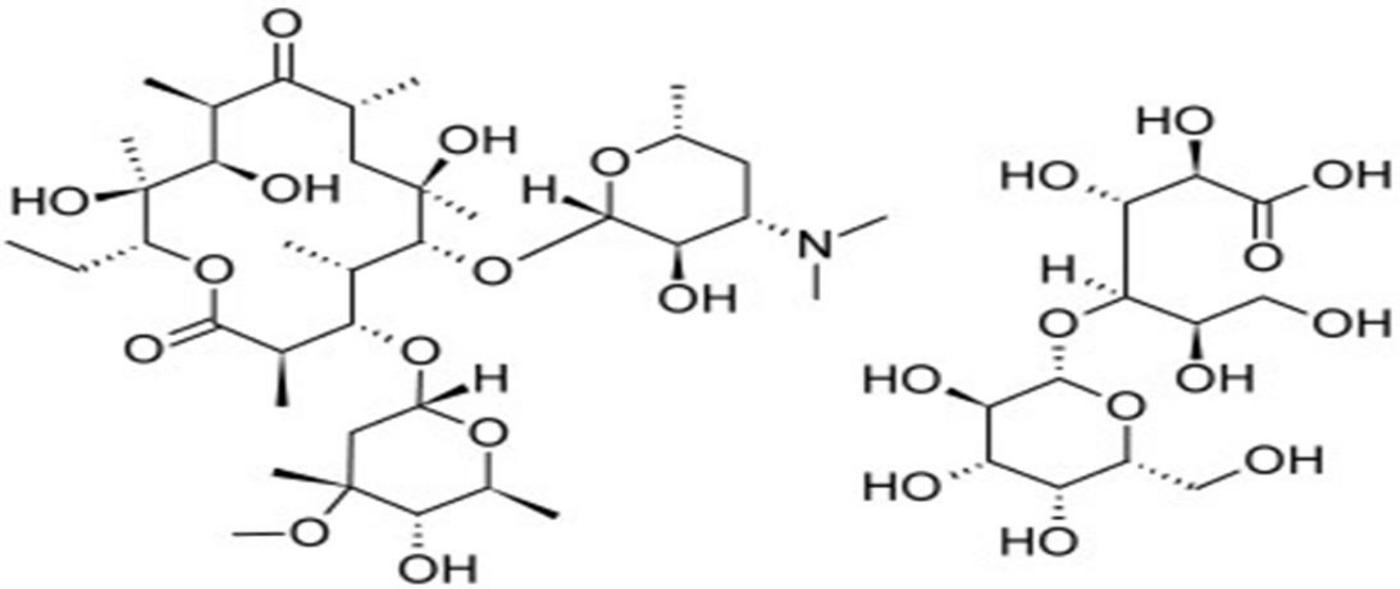
1.Acid salts of the dimethyl amino group

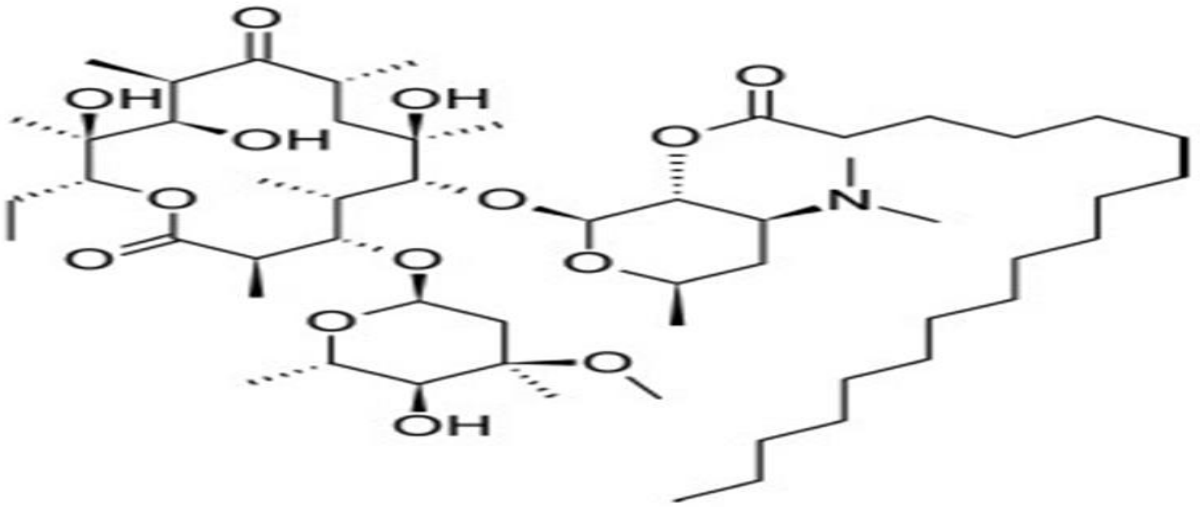
Erythromycin Lactobionate

Erythromycin lactobionate is a water-soluble salt prepared by reacting erythromycin base with lactobiono-ð-lactone



2.Esters of the 2`-hydroxyl group

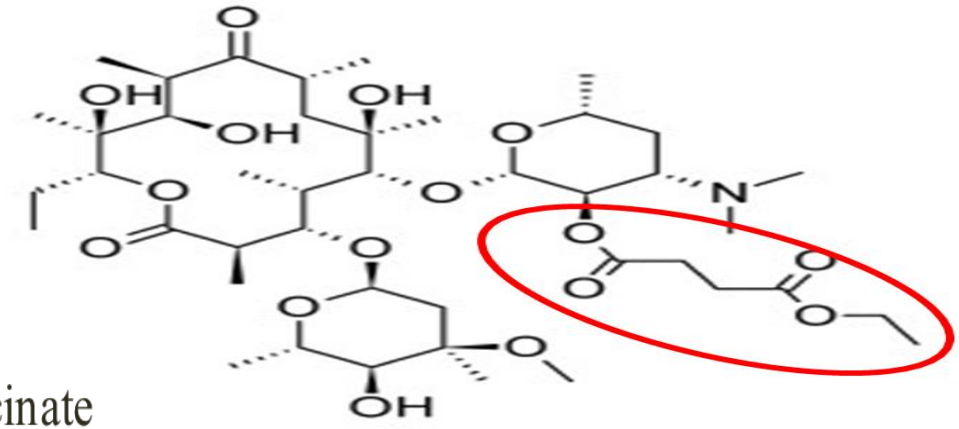
Erythromycin stearate : is the stearic acid salt of erythromycin. It is film coated to protect it from acid degradation in the stomach. In the alkaline pH of the duodenum, the free base is liberated from the stearate and absorbed



Erythromycin Stearate

Erythromycin Ethylsuccinate is the Ethylsuccinate mixed ester of erythromycin in which the 2`-hydroxyl group of the desosamine is esterified.

It is absorbed as the ester and hydrolyzed slowly in the body to form erythromycin.

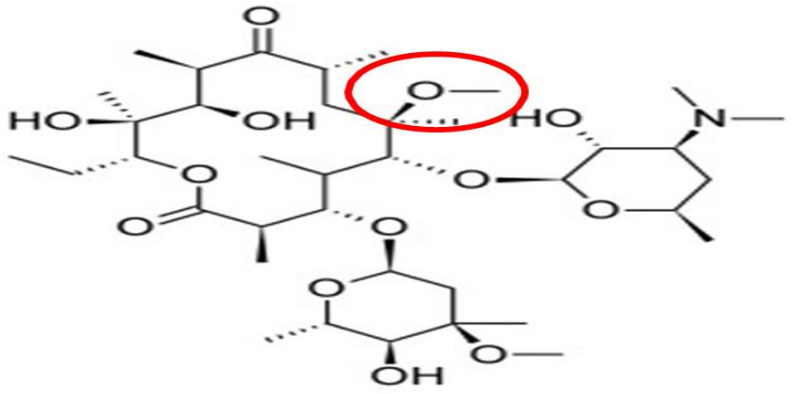


Erythromycin Ethylsuccinate

3.Methylation of the 6-hydroxyl group:

Clarithromycin

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.

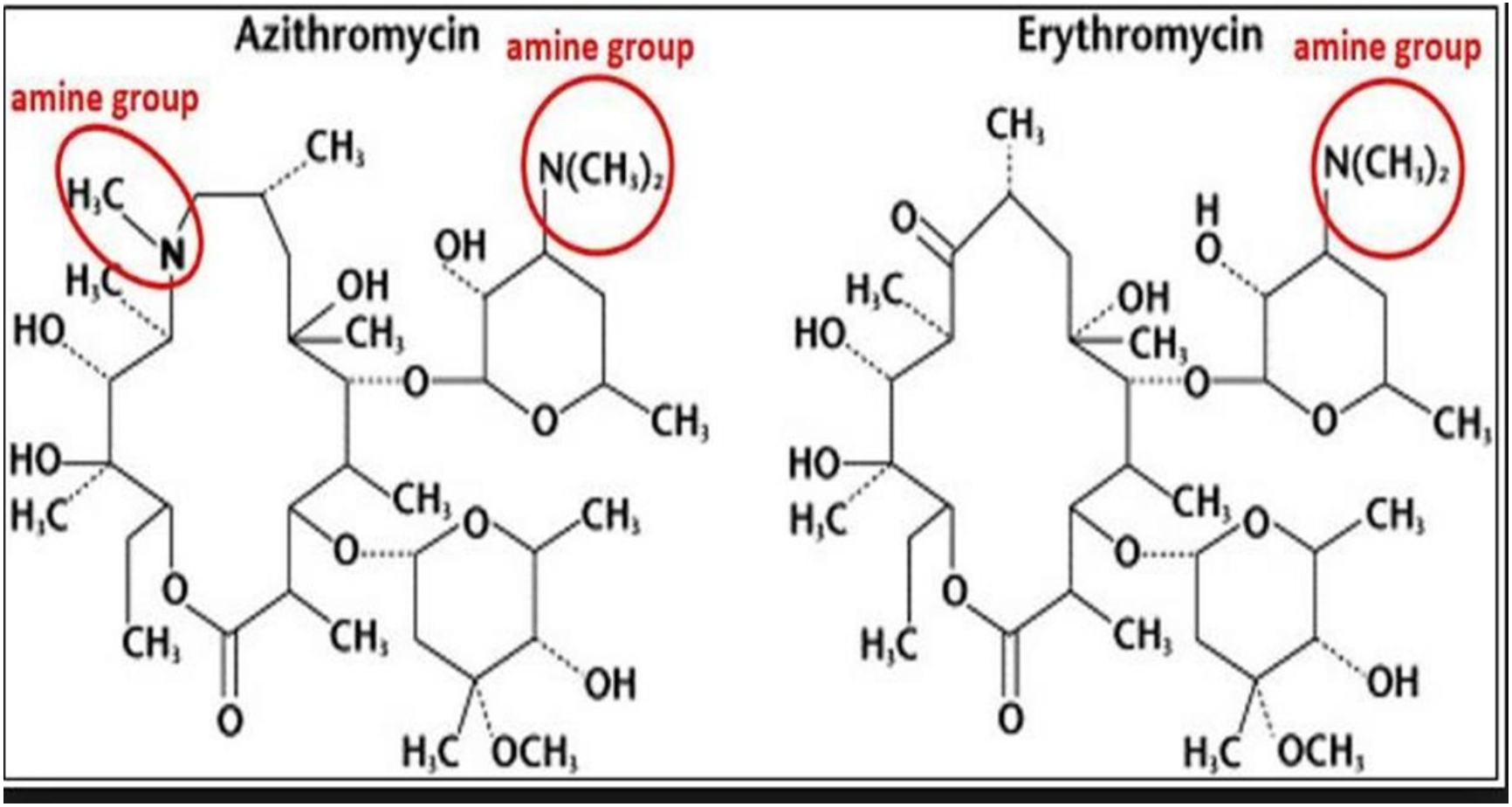


Azithromycin

Azithromycin (Zithromax) is a semisynthetic derivative of erythromycin, prepared by Beckman rearrangement of the corresponding oxime, followed by N methylation and reduction of the resulting ring-expanded lactam.

It is a prototype of a series of nitrogen-containing, 15-membered ring macrolides known as azalides.

Removal of the 9-keto group coupled with incorporation of a weakly basic tertiary amine nitrogen function into the macrolide ring increases the stability of azithromycin to acid-catalyzed degradation



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

Oleandomycin, as its triacetyl derivative. Its structure consists of two sugars and a 14-member lactone ring designated an oleandolide.

One of the sugars is desosamine, also present in erythromycin; the other is L- oleandrose.

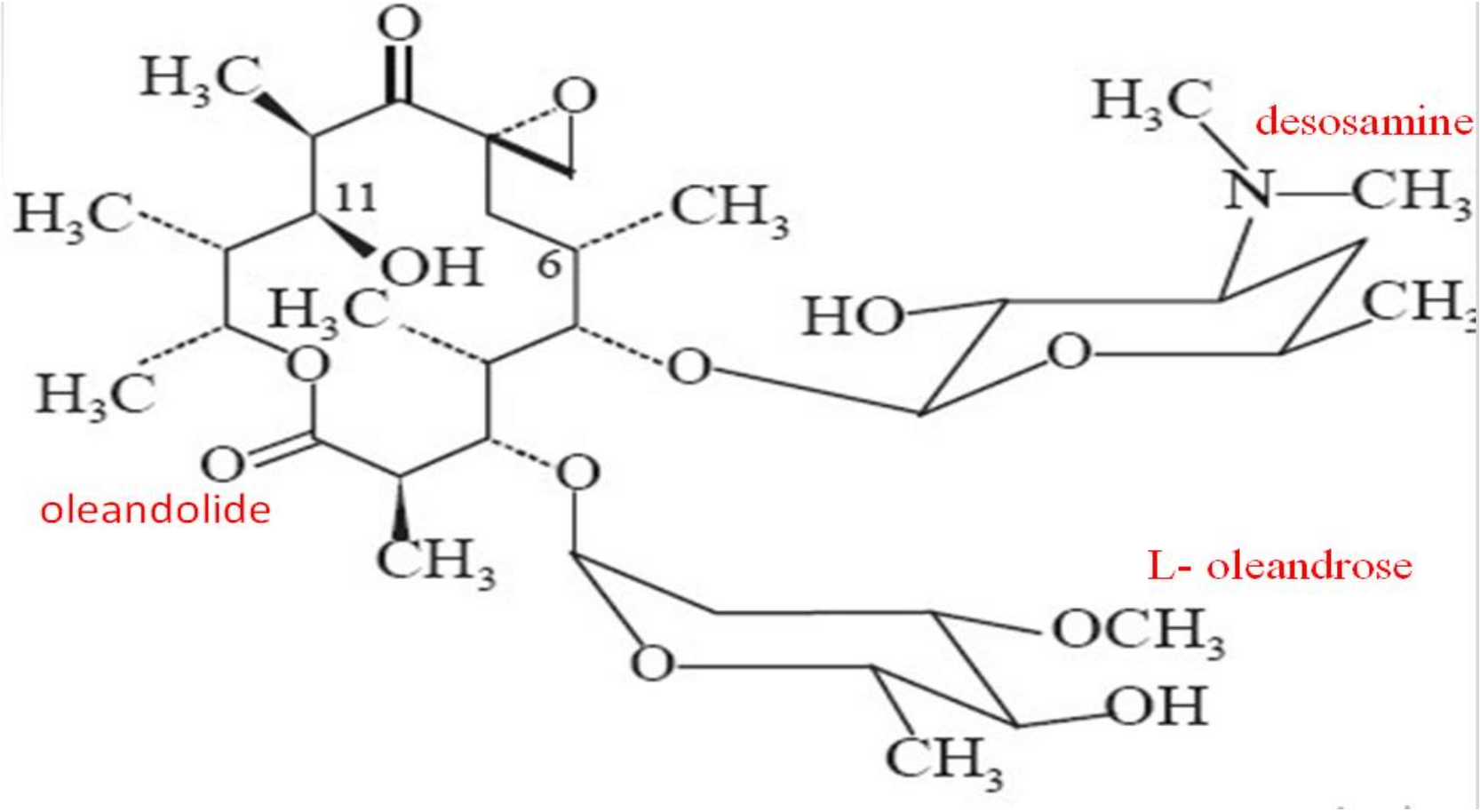
The sugars are linked glycosidically to the positions 3 and 5, respectively, of oleandolide.

Oleandomycin contains three hydroxyl groups that are subject to acylation, one in each of the sugars and one in the oleandolide.

The triacetyl derivative retains the in vivo antibacterial activity of the parent antibiotic but possesses superior pharmacokinetic properties.

It is hydrolyzed in vivo to oleandomycin

Oleandomycin



Telithromycin

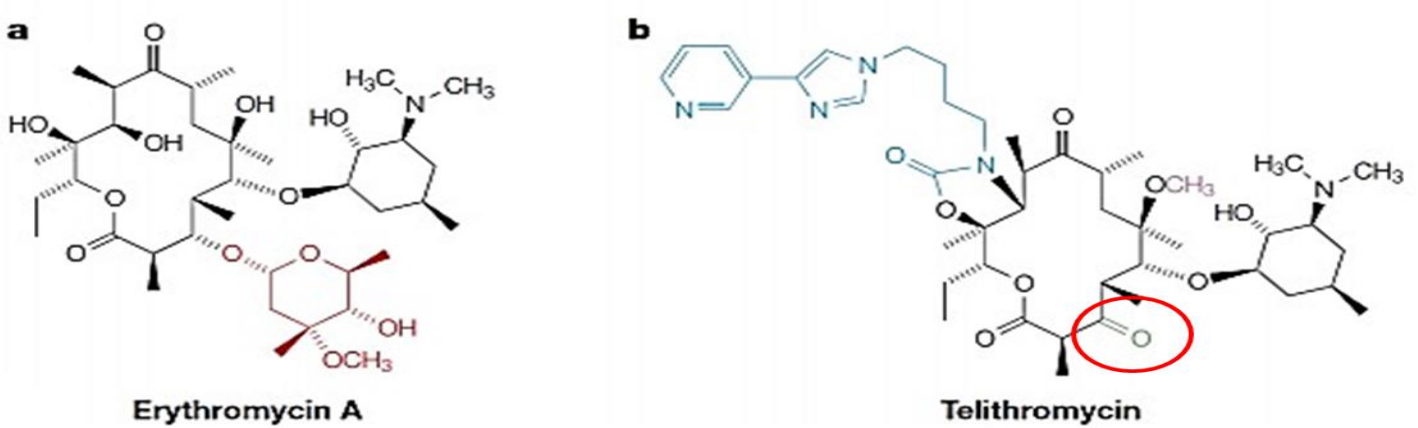
Is a semi-synthetic derivative of erythromycin and reached the European market in 2001. The cladinose sugar in erythromycin has been replaced with a keto-group and a carbamate ring has been fused to the macrocyclic ring.

The two hydroxyl groups that cause the intramolecular ketal formation in erythromycin have been masked, one as a methoxy group and the other as part of the carbamate ring.

To improve the activity and pharmacokinetics a carbamate side chain and a methoxy group were added.

The methoxy group leads to the stability of Telithromycin in the acid medium in the stomach

Telithromycin prevents bacterial growth by inhibiting protein synthesis. It binds to the 23S rRNA and the 50S ribosomal subunit domain, causing the deactivation of metabolic processes. Its binding affinity is 10 times higher than that of Erythromycin, making it far more effective drug against resistant strains.



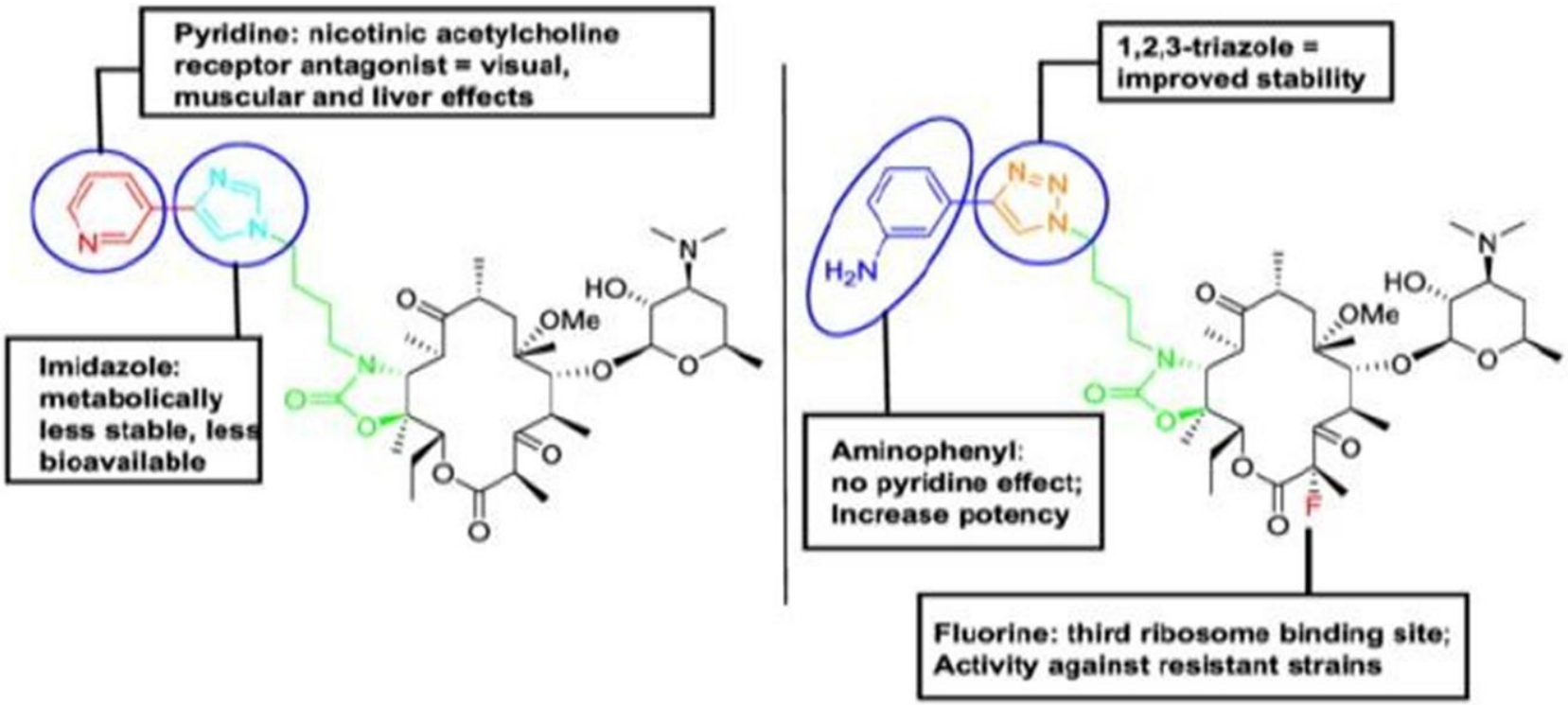
. Differences between Erythromycin A and Telithromycin

side effects of Telithromycins

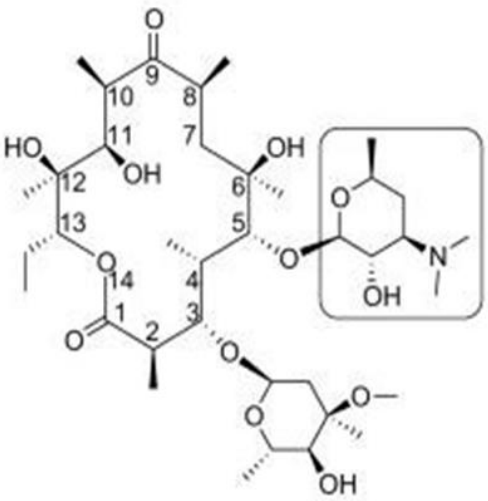
Telithromycin's side chain pyridine moiety blocks nicotinic acetylcholine receptors located in the neuromuscular junction, the ciliary ganglion of the eye and the vagus nerve innervating the liver causing uncommon but severe side effects including hallucinations, diplopia and liver failure.

New macrolides such as azithromycin, clarithromycin and the fluoro ketolide, Solithromycin contain a different side chain, as well as a fluorine substituent. These alterations not only positively affect the stability of the macrolide but also do not interfere with the choline dependent receptors as severely as Telithromycin does, thus causing less severe side effects

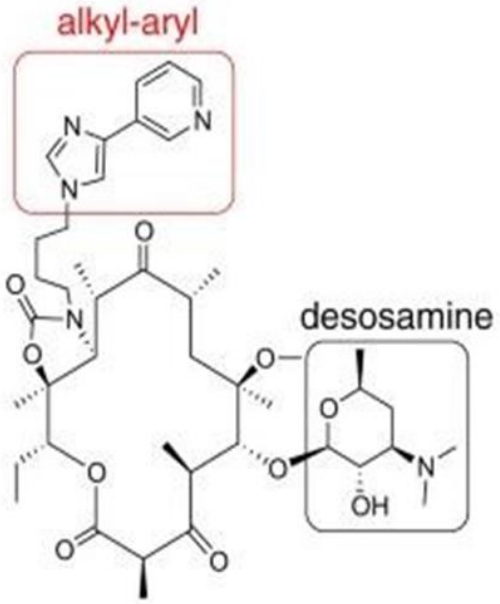
Telithromycin versus Solithromycin



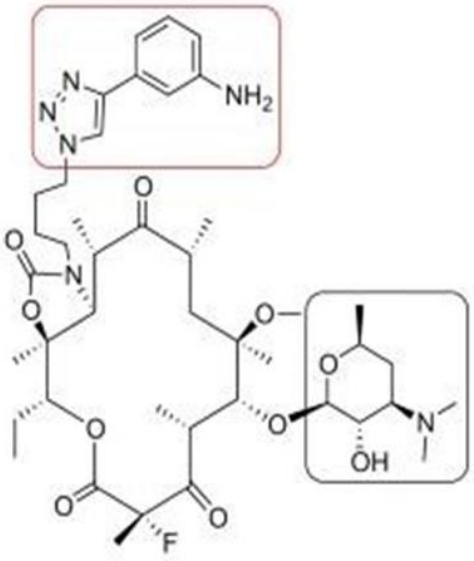
Erythromycin
(ERY)



Telithromycin
(TEL)



Solithromycin
(SOL)



Lincomycins

The lincomycins are sulfur-containing antibiotics isolated from Streptomyces lincolnensis. Lincomycin is the most active and medically useful of the compounds obtained from fermentation.

Extensive efforts to modify the lincomycin structure to improve its antibacterial and pharmacological properties resulted in the preparation of the 7-chloro-7-deoxy derivative Clindamycin.

Clindamycin appears to have the greater antibacterial potency and better pharmacokinetic properties.

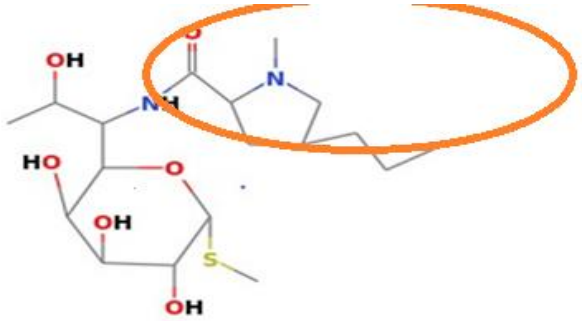
Lincomycins resemble macrolides in antibacterial spectrum and biochemical mechanisms of action.

Lincomycin-related antibiotics differ in structure at one or more of three positions of the lincomycin structure:

(a) the N-methyl of the hygric acid moiety is substituted by a hydrogen

(b) the n-propyl group of the hygric acid moiety is substituted by an ethyl group

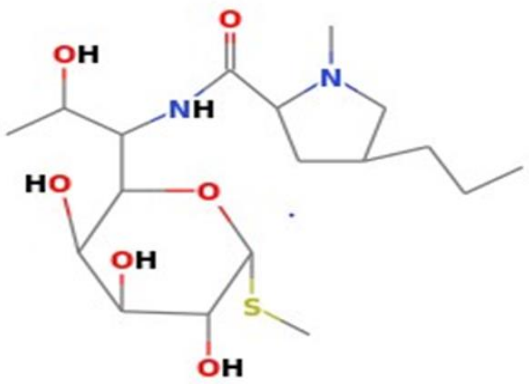
(c) the thiomethyl ether of theα-thiolincosamide moiety is substituted by a thioethyl ether.



Lincomycin Hydrochloride

The structure contains a basic function, the pyrrolidine nitrogen, by which water-soluble salts. Lincomycin binds to the 50S ribosomal subunit to inhibit protein synthesis. Its action may be bacteriostatic or bactericidal depending on various factors, including the concentration of the antibiotic.

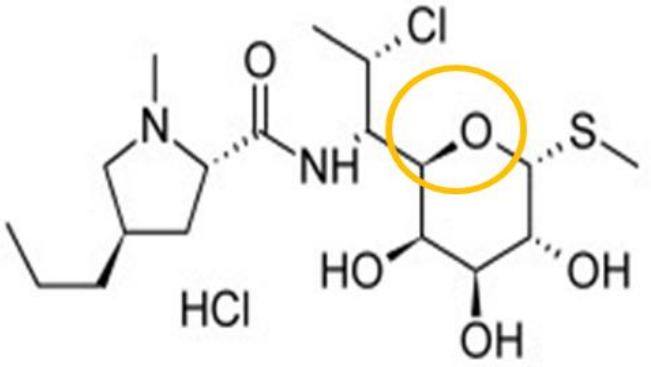
When subjected to hydrazinolysis, lincomycin is cleaved at its amide bond



Clindamycin Hydrochloride

Replacement of the 7(R)-hydroxy group of lincomycin by chlorine with inversion of configuration resulted in a compound with enhanced antibacterial activity in vitro. Clinical experience with this semisynthetic derivative, clindamycin, 7(S)-chloro-7-deoxylincomycin (Cleocin), released in 1970, has established that its superiority over lincomycin is even greater in vivo.

Improved absorption and higher tissue levels of clindamycin and its greater penetration into bacteria have been attributed to a higher partition coefficient than that of lincomycin



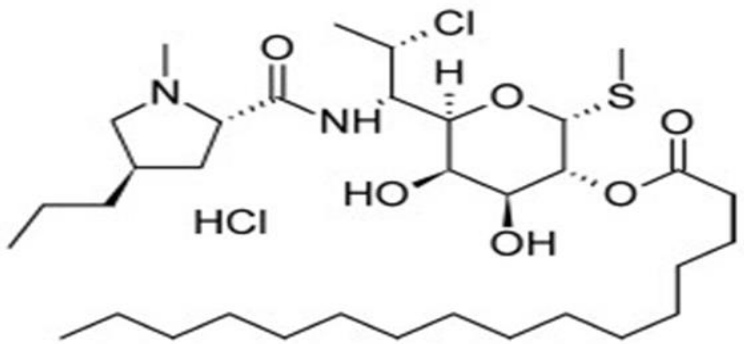
Structural modifications of Lincomycins

- Structural modifications at C-7 as 7(S)-chloro

and 7(R)-OCH3) and of the C-4 alkyl groups of the hygric acid moiety appear to influence activity of congeners more through an effect on the partition coefficient of the molecule than through a stereospecific binding role.

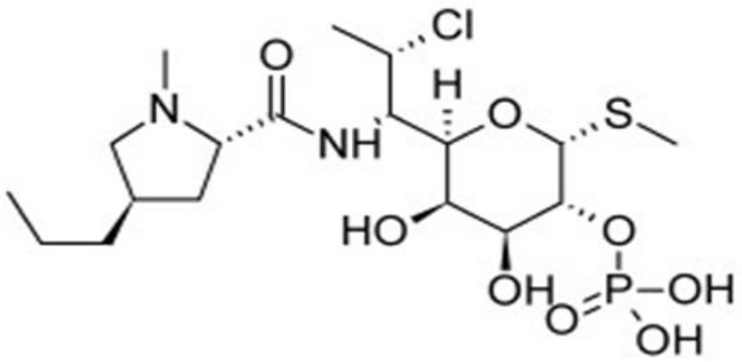
- Changes in the α-thiolincosamide portion of the molecule seem to decrease activity markedly, however, as evidenced by the marginal activity of 2-deoxylincomycin, its anomer, and 2- O- methyl lincomycin.

- Exceptions to this are fatty acid and phosphate esters of the 2-hydroxyl group of lincomycin and clindamycin, which are hydrolyzed rapidly in vivo to the parent antibiotics.



Clindamycin Palmitate Hydrochloride

(The ester bond is to the 2-hydroxyl group of the lincosamine sugar.)



Clindamycin phosphate

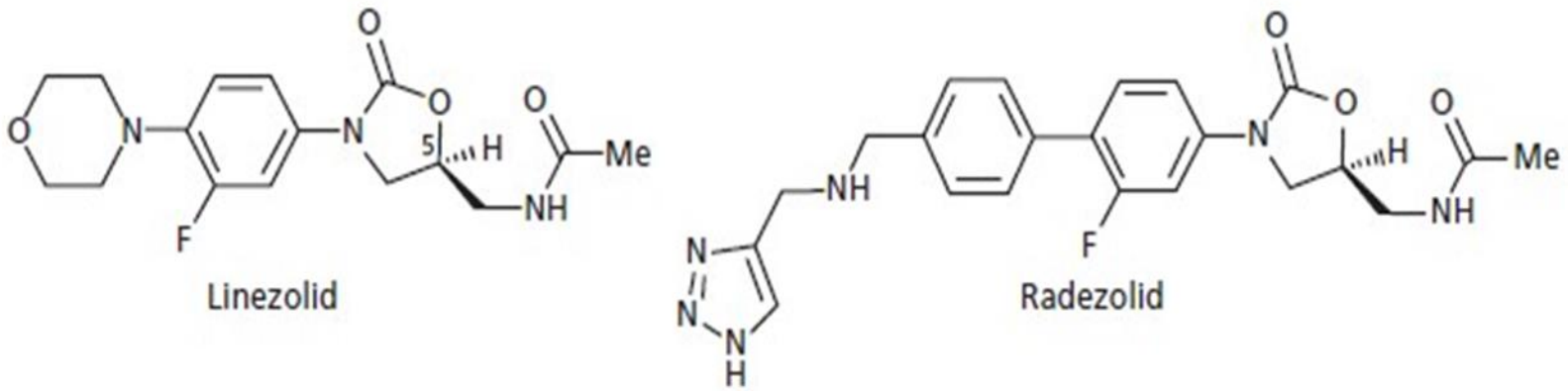
(The 2-phosphate ester of clindamycin.)

Oxazolidinones

The oxazolidinones are a new class of synthetic antibacterial agents discovered in recent years. They inhibit protein synthesis at a much earlier stage than previous agents, and, consequently, do not suffer the same resistance problems. Before protein synthesis can start, a 70S ribosome has to be formed by the combination of a 30S ribosome with a 50S ribosome.

The oxazolidinones bind to the 50S ribosome and prevent this from happening.Linezolid was the first of this class of compounds to reach the market in 2000.

X-ray crystallographic studies have revealed how the structure binds to the ribosome, and that has allowed the development of analogues which bind more strongly. Radezolid is one such structure which binds10,000 times more strongly as a result of extra binding interactions. It is currently undergoing clinical trials.



Oxazolidinones.

Polypeptides

Among the most powerful bactericidal antibiotics are those that possess a polypeptide structure. Antibiotics of the polypeptide class differ widely in their mechanisms of action and antimicrobial properties.

Bacitracin and vancomycin interfere with bacterial cell wall synthesis and are effective only against Gram-positive bacteria.

Neither antibiotic apparently can penetrate the outer envelope of Gram-negative bacteria.

Both the gramicidins and the polymyxins interfere with cell membrane functions in bacteria. However, the gramicidins are effective primarily against Gram-positive bacteria, whereas the polymyxins are effective only against Gram-negative species

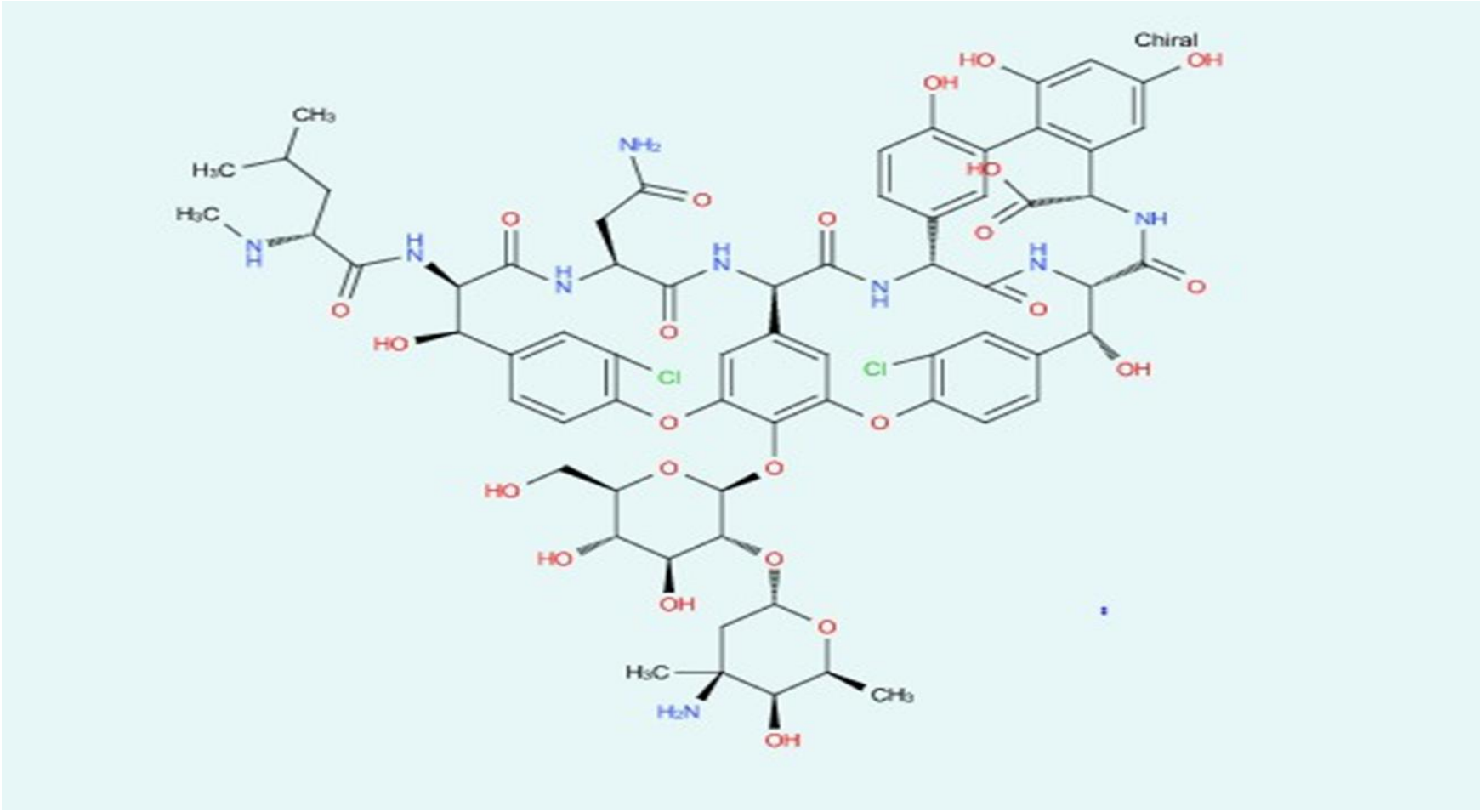
The polypeptide antibiotic polymyxin B derives from a soil bacterium called Bacillus polymyxa .

It also operates within the cell membrane and shows a selective toxicity for bacterial cells over animal cells.

This appears to be related to the ability of the compound to bind selectively to the different plasma membranes.

The mechanism of this selectivity is not fully understood. Polymyxin B acts like valinomycin but it causes the leakage of small molecules such as nucleosides from the cell.

Vancomycin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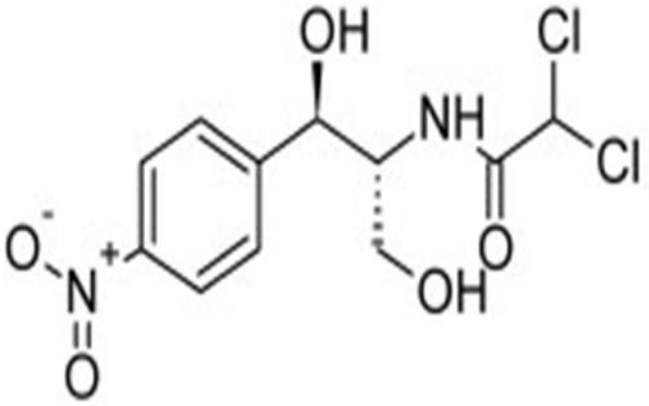
Unclassified antibiotics Chloramphenicol

The first of the widely used broad-spectrum antibiotics. It possesses two chiral carbon atoms.

Numerous structural analogs of chloramphenicol have been synthesized to provide a basis for correlation of structure to antibiotic action



- It appears that the p-nitro phenyl group may be replaced by other aryl structures without appreciable loss in activity.
- Substitution on the phenyl ring with several different types of groups for the nitro group, a very unusual structure in biological products, does not greatly decrease activity. All such compounds yet tested are less active than chloramphenicol.
- Modification of the side chain shows that it possesses high specificity in structure for antibiotic action.
- Conversion of the alcohol group on C-1 of the side chain to a keto group causes appreciable loss in activity

- Chloramphenicol binds to the 50S subunit of ribosomes and appears to act by inhibiting the movement of ribosomes along mRNA, probably by inhibiting the peptidyl transferase reaction by which the peptide chain is extended. Since it binds to the same region as macrolides combination.
- The nitro group and both alcohol groups are involved in binding interactions.
- The dichloroacetamide group is also important, but can be replaced by other electronegative groups.
- Chloramphenicol is quite toxic and the nitro substituent is thought to be responsible for this. and lincosamides , these drugs cannot be used in combination.