Pharmaceutical chemistry
Antibacterial Antibiotics
Macrolides, Lincomycins, Oxazolidinones, Polypeptides and Unclassified antibiotics
Chloramphenicol

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Macrolides

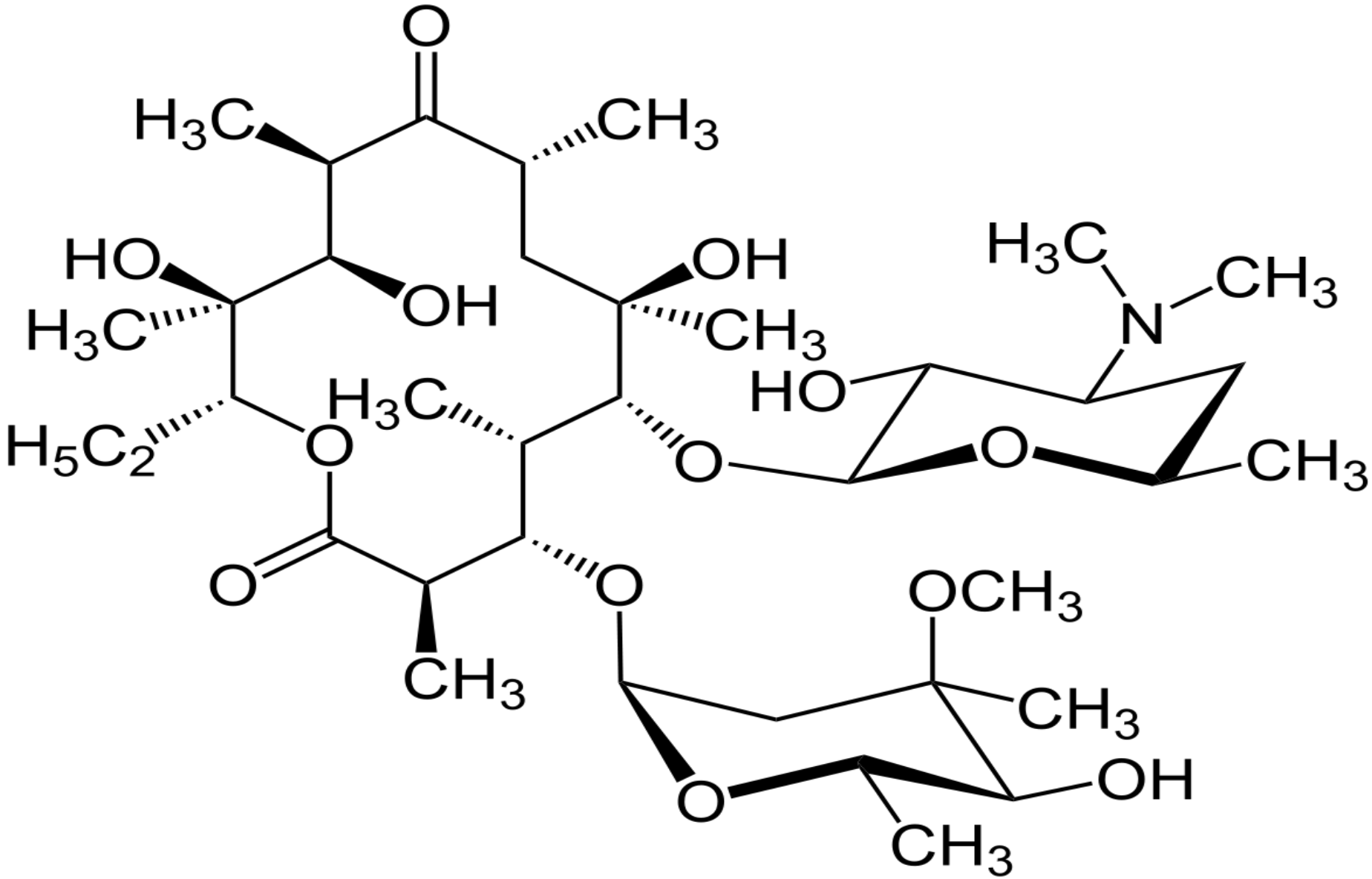
- The macrolide antibiotics have three common chemical characteristics:

(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.


O
H3C
CH3
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N
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O
O
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OCH3
CH3
OH
O
CH3

Mechanism of Action and Resistance

- Macrolides bind 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.

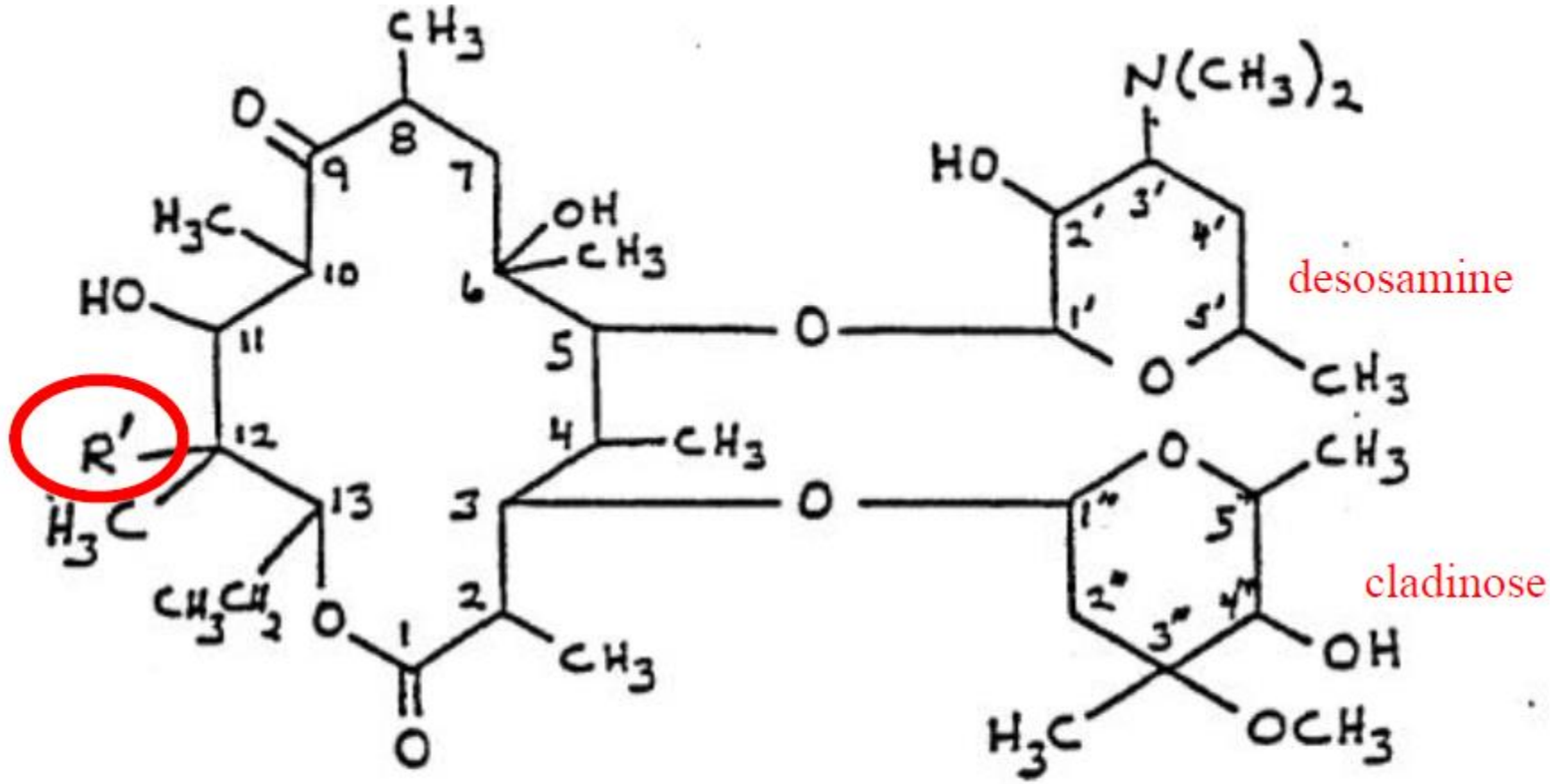
Spectrum of Activity

- 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, and exhibit useful effectiveness against Gram-negative cocci, especially Neisseria.

Products
Erythromycin

- The commercial product is erythromycin A, which differs from its biosynthetic precursor, erythromycin B, in having a hydroxyl group at the 12-position of the aglycone.
- 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 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 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 has been chemically modified with primarily two different goals in mind:

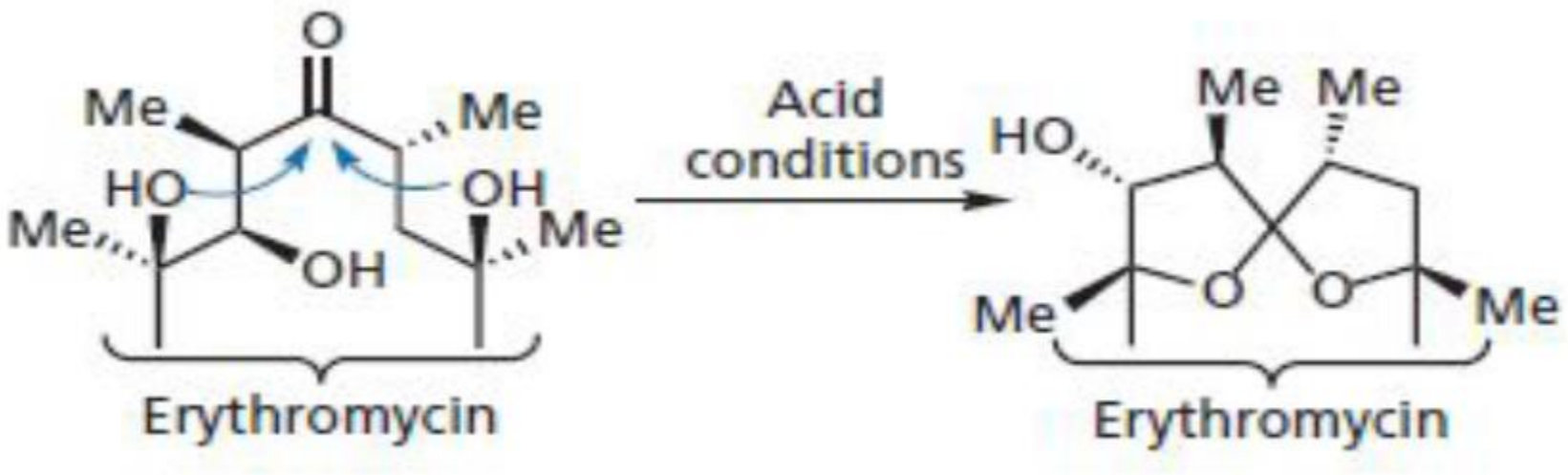
(a) Increase either its water or its lipid solubility for parenteral dosage forms and

(b) 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.

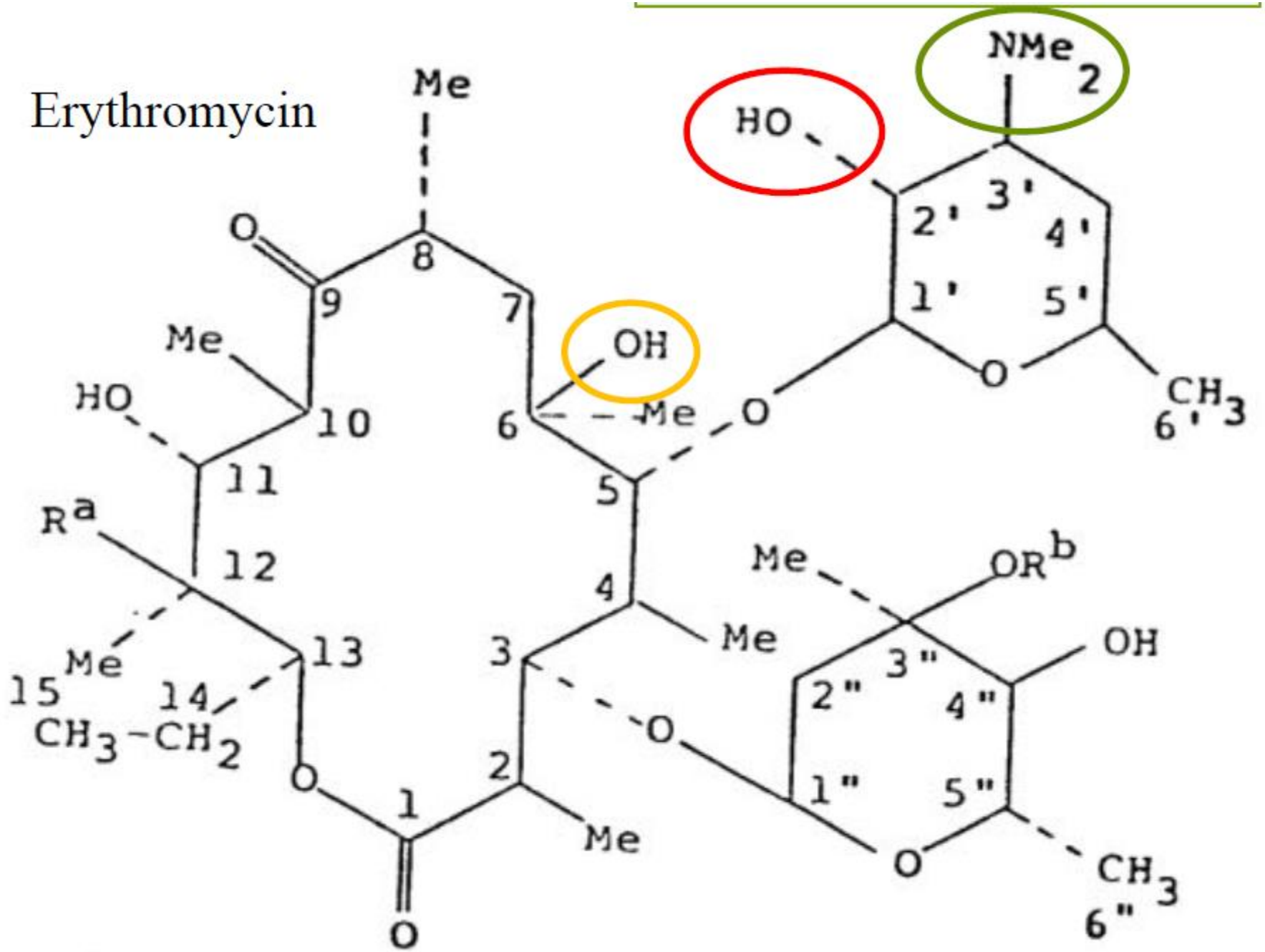
- Modified derivatives of the antibiotic are of two types:

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).

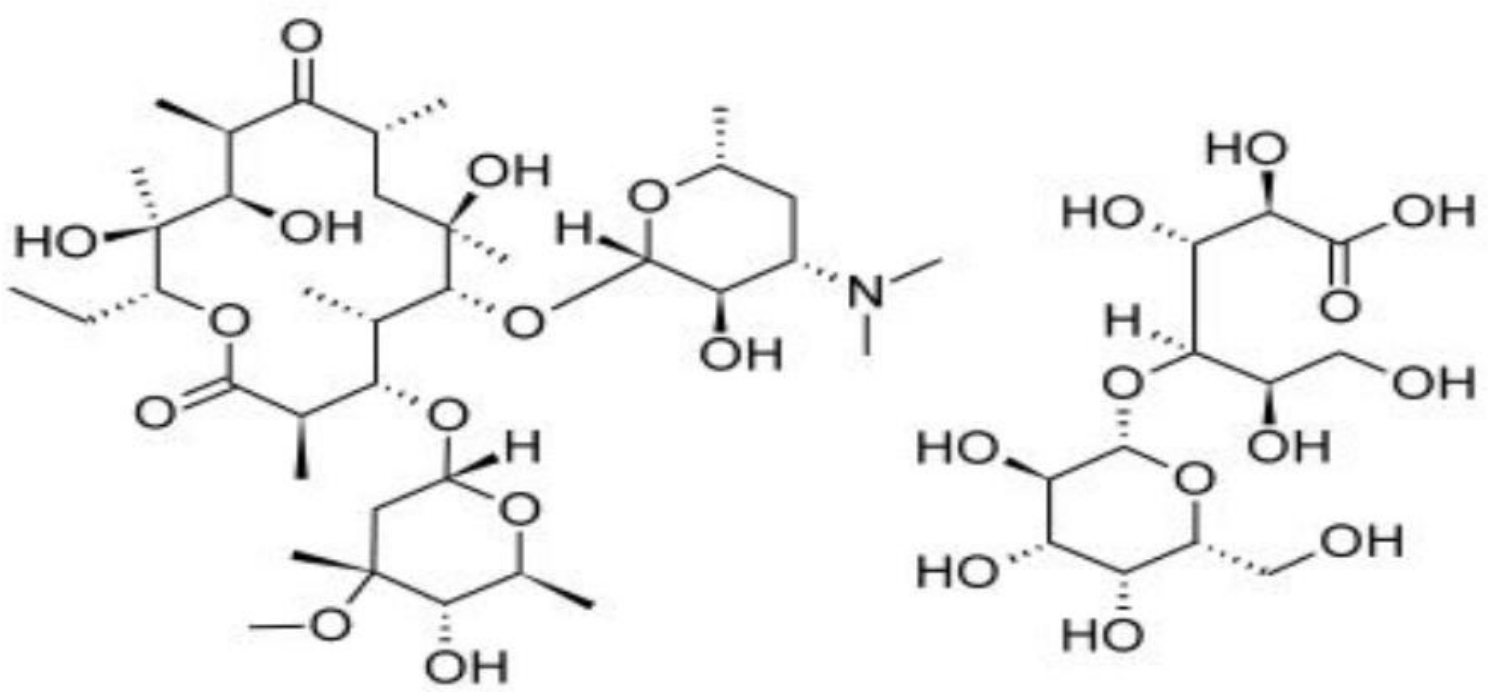
- The stearate salt and the ethylsuccinate and propionate esters are used in oral dose forms intended to improve absorption of the antibiotic. The stearate releases erythromycin base in the intestinal tract, which is then absorbed.

Erythromycin



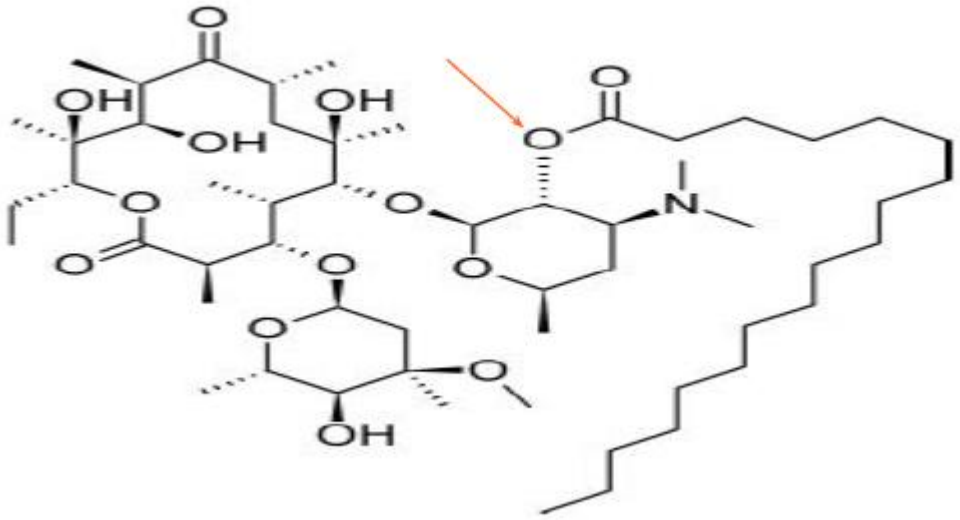
1. Acid salts of the dimethyl amino group: Erythromycin Lactobionate

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



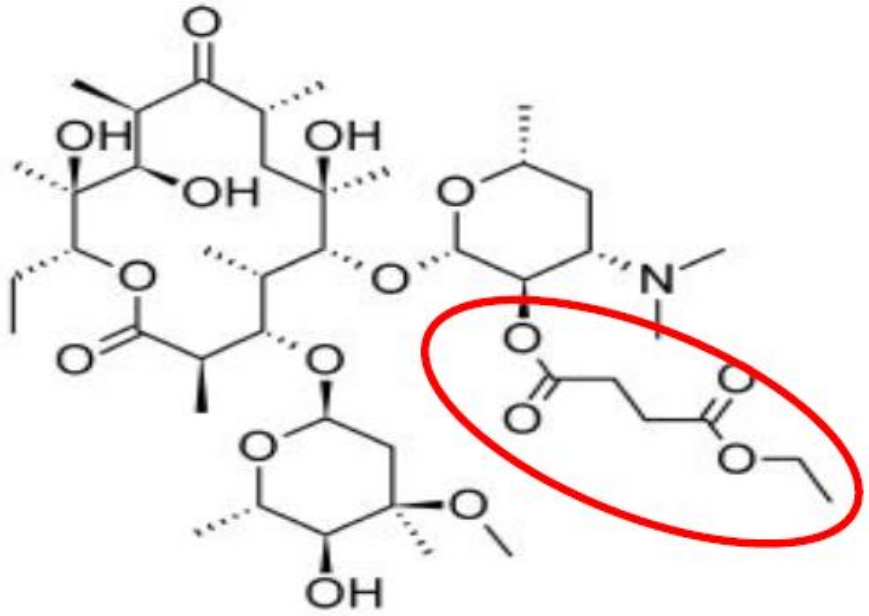
2. Esters of the 2`-hydroxyl group

- 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.

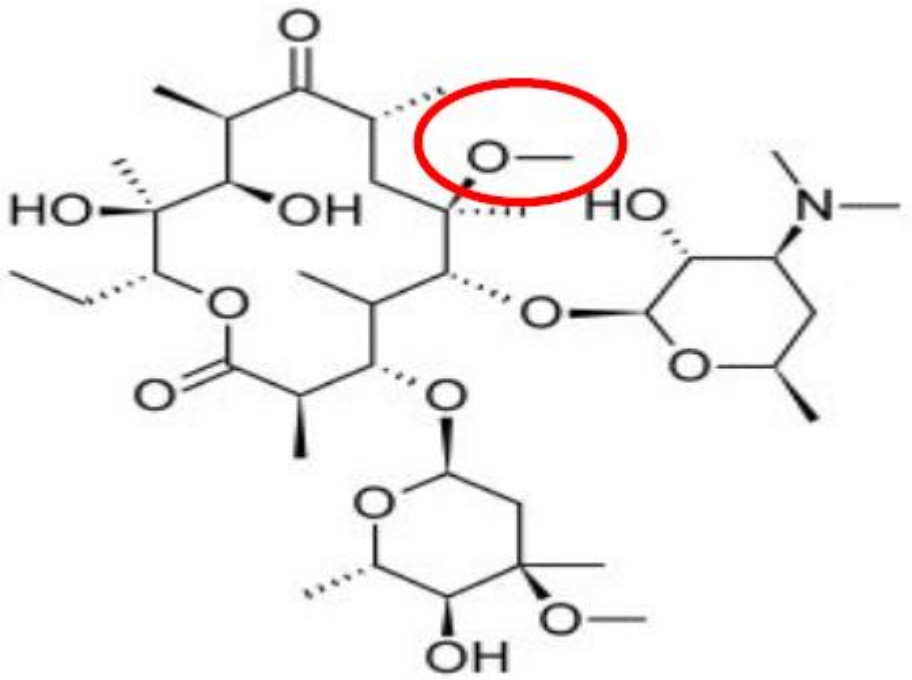


- Erythromycin Ethylsuccinate

3. Methylation of the 6-hydroxyl group: Clarithromycin

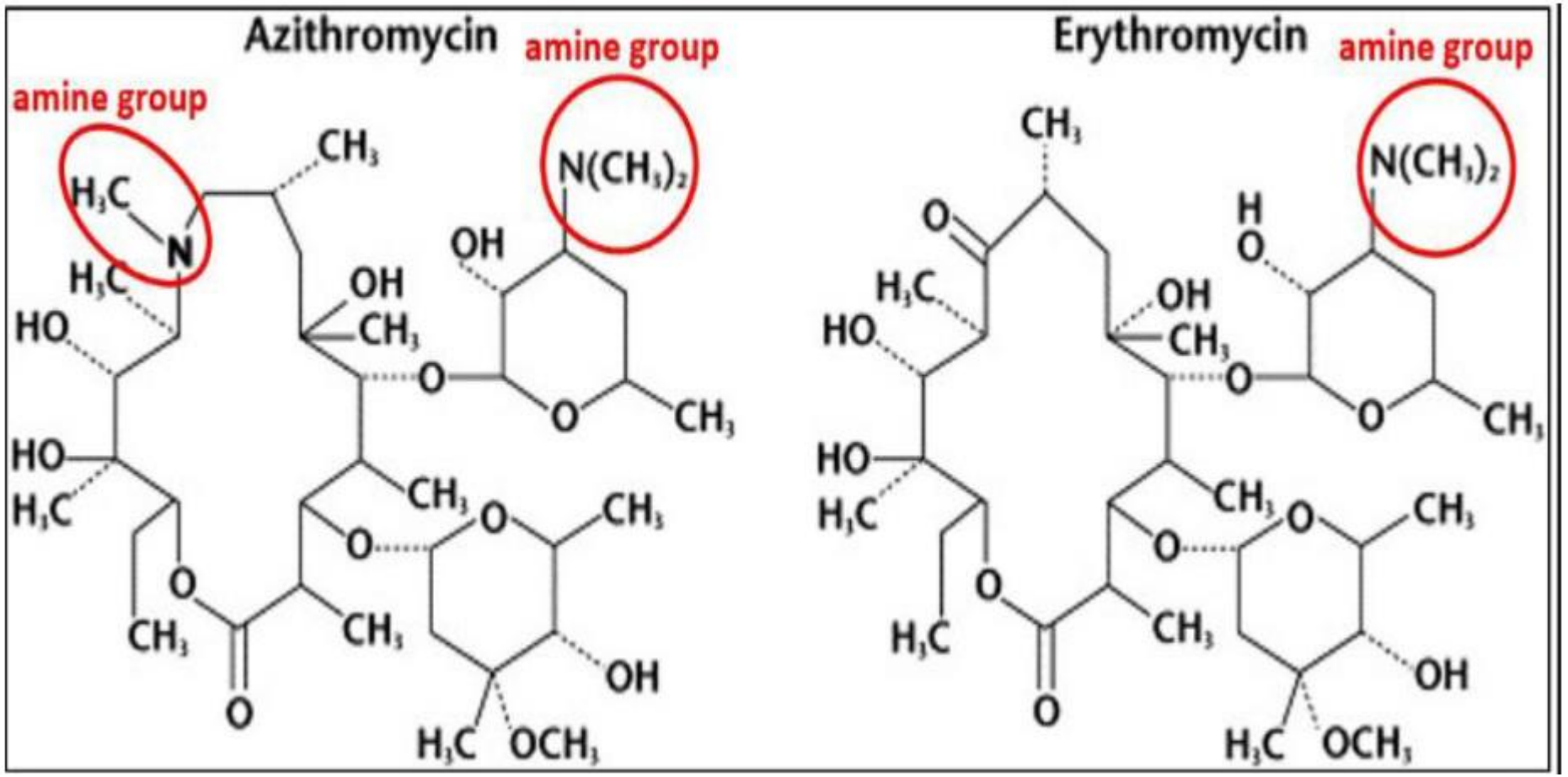
- The simple methylation of the 6-hydroxyl group of erythromycin creates a semisynthetic derivative that fully retains the antibacterial properties of the parent antibiotic, with markedly increased acid stability and oral bioavailability and reduced GI side effects associated with erythromycin.

- Clarithromycin



Azithromycin

- Azithromycin 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

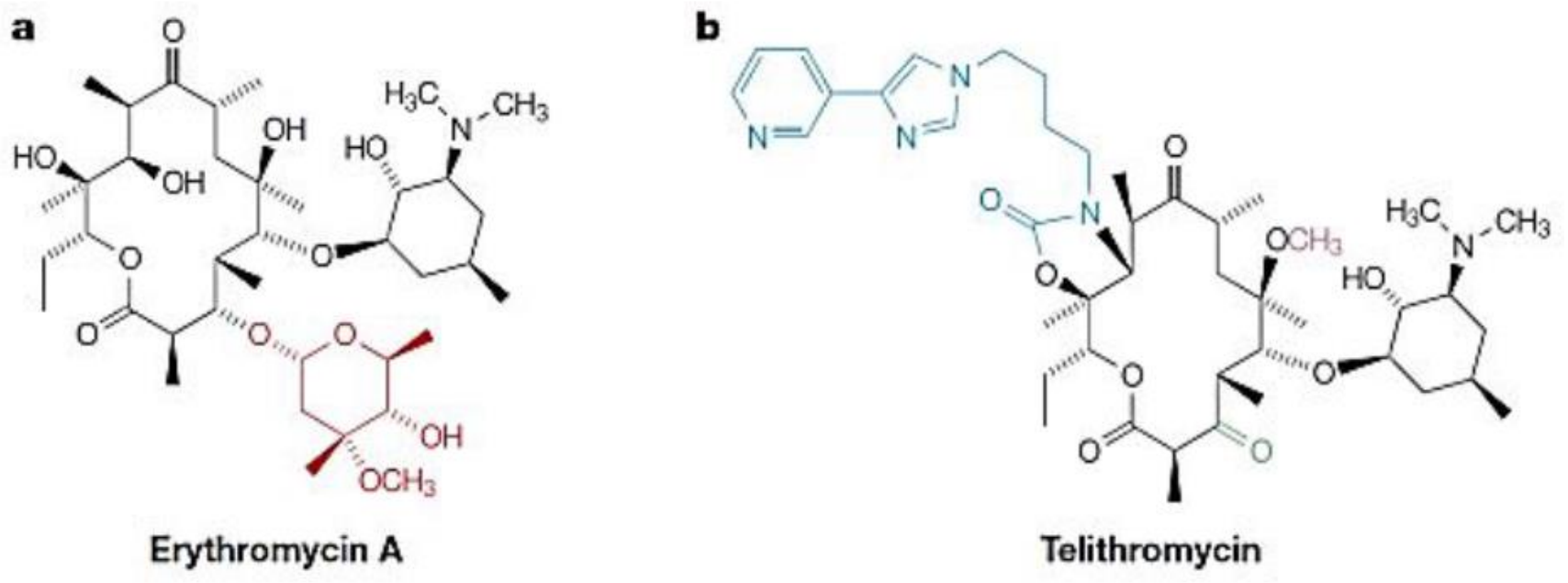


- These changes also increase the lipid solubility of the molecule, thereby conferring unique pharmacokinetic and microbiological properties

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

- Telithromycin binding affinity is 10 times higher than that of Erythromycin, making it far more effective drug against resistant strains.

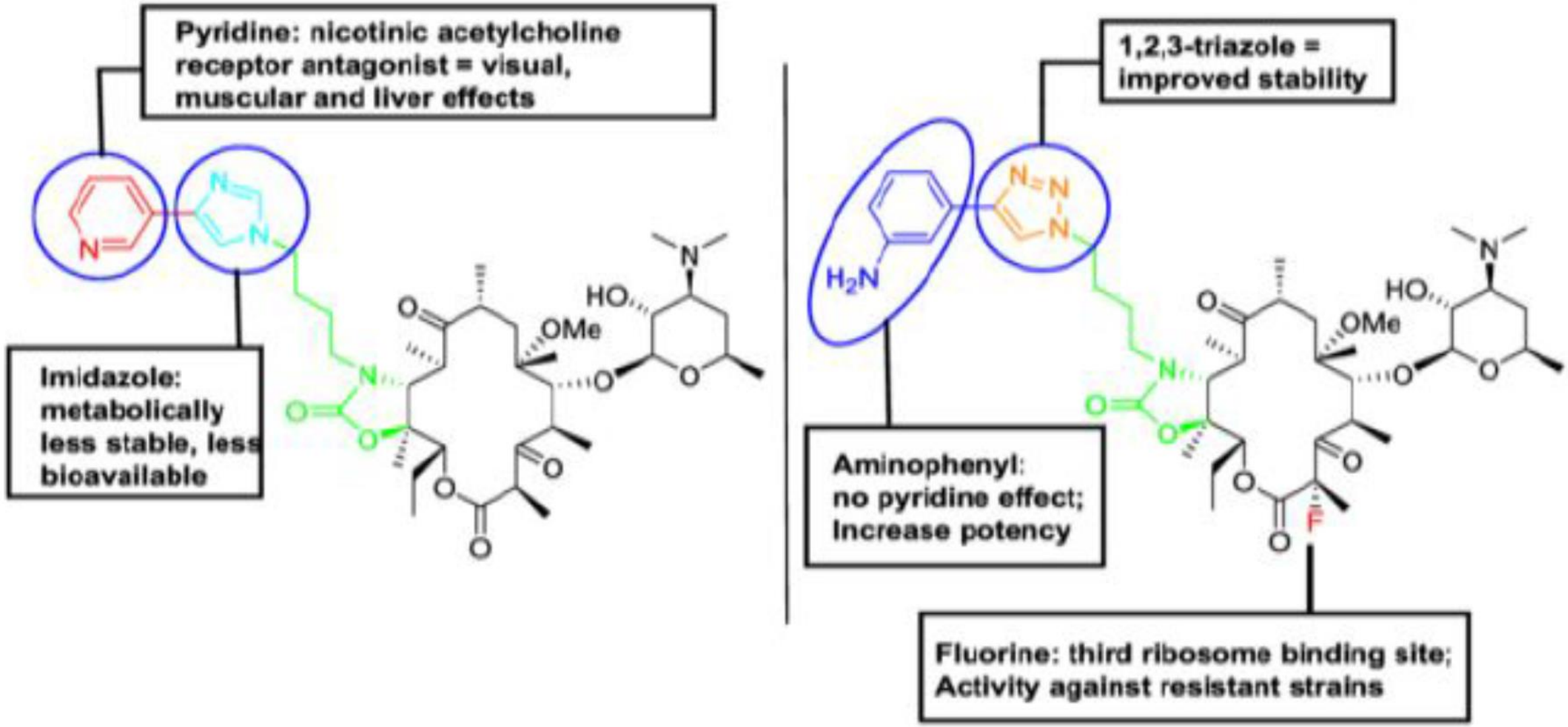


. Differences between Erythromycin A and Telithromycin

Causes of severe side effects

- 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



Lincomycins

- The lincomycins are sulfur-containing antibiotics isolated from Streptomyces.
- 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.

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

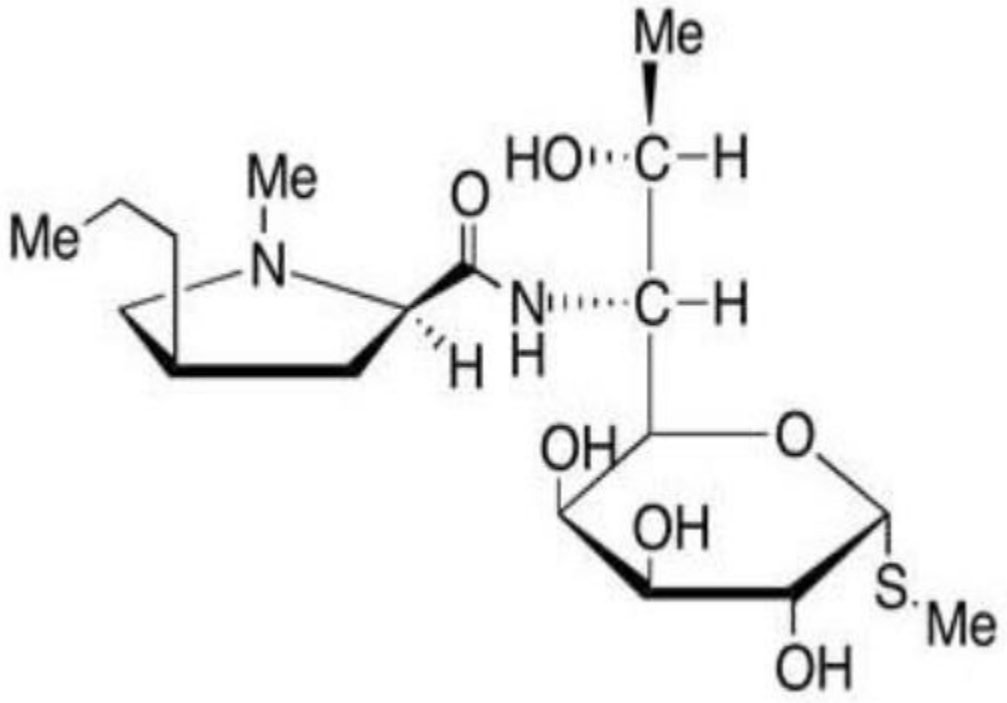
(a) the N-methyl of the hygric acid moiety is substituted by a hydrogen

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

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

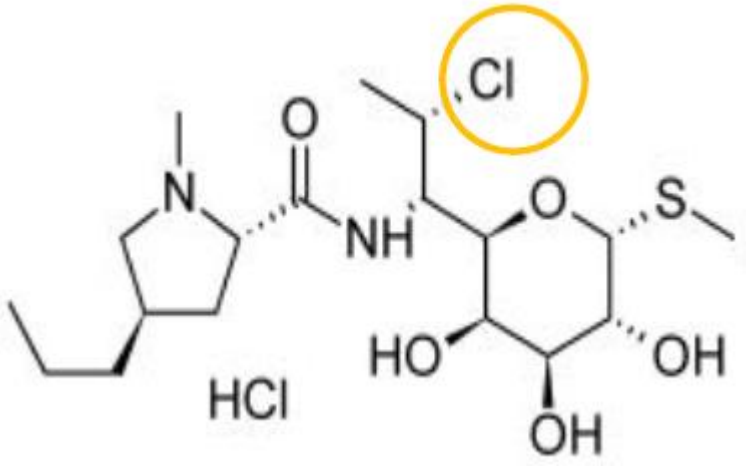
Lincomycin Hydrochloride

- The structure contains a basic function, the pyrrolidine nitrogen, by which water-soluble salts with an apparent pKa of 7.6 may be formed.



Clindamycin Hydrochloride

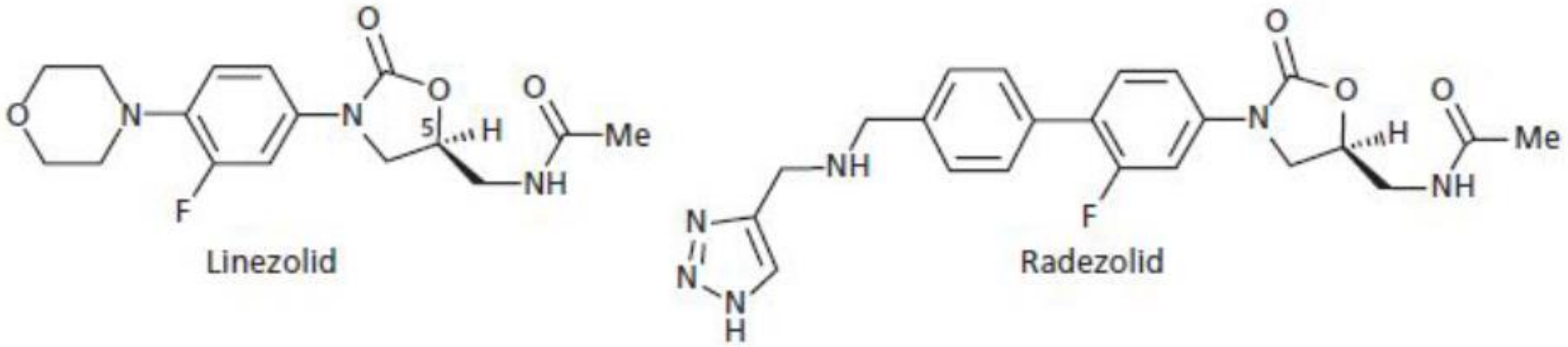
- Replacement of the 7(R)-hydroxy group of lincomycin by chlorine with inversion of configuration resulted in a compound with enhanced antibacterial activity in vitro.
- Improved absorption and higher tissue levels of clindamycin and its greater penetration into bacteria have been attributed to a higher partition coefficient than that of lincomycin.



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. As a result, translation cannot even start.
- Other agents that inhibit protein synthesis do so during the translation process itself .Linezolid was the first of this class of compounds.

- Radezolid is one such structure which binds 10,000 times more strongly as a result of extra binding interactions. It is currently undergoing clinical trials.



.Oxazolidinones

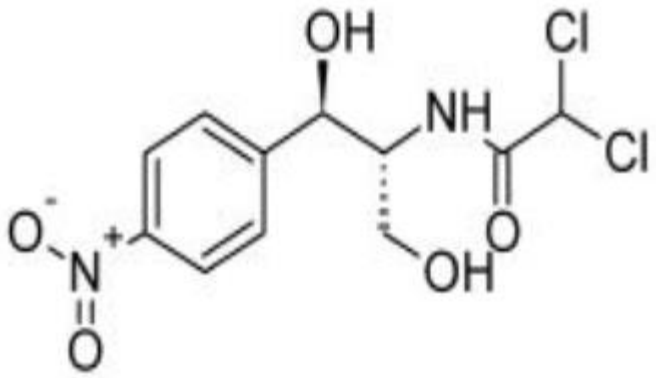
Polypeptides

- 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.

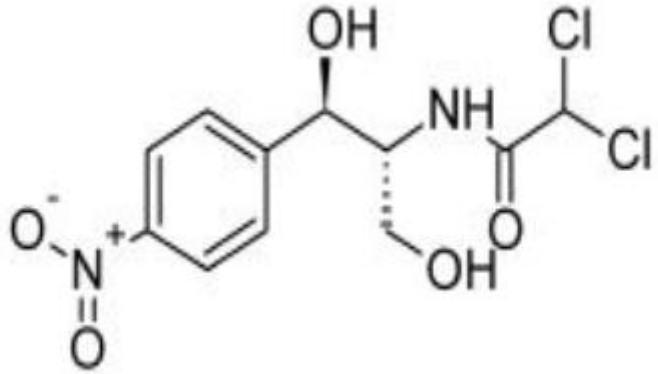
- polymyxin B operates within the cell membrane and shows a selective toxicity for bacterial cells over animal cells. This appears to be related to the ability of the compound to bind selectively to the different plasma membranes. The mechanism of this selectivity is not fully understood.
- Polymyxin B acts like valinomycin, but it causes the leakage of small molecules such as nucleosides from the cell.

Unclassified antibiotics
Chloramphenicol

- The first of the widely used broad-spectrum antibiotics. It possesses two chiral carbon atoms in the chain. Biological activity resides almost exclusively in the D-threo isomer.



- 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.
- Conversion of the alcohol group on C-1 of the side chain to a keto group causes appreciable loss in activity.



- The metabolism of chloramphenicol has been investigated thoroughly.
- The main path involves:

➢formation of the 3-O-glucuronide.

➢Minor reactions include reduction of the p-nitro group to the aromatic amine

➢hydrolysis of the amide, and hydrolysis of the -chloracetamido group, followed by reduction to give the corresponding –hydroxyacetyl derivative.

THANK YOU

- ANY QUESTIONS??

Rest for 15 minutes