Subject: Medicinal Chemistry-III

Topic: Macrolide Antibiotic (Erythromycin, Clarithromycin, Azithromycin)

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MACROLIDES:

- The macrolides are a group of antibiotics produced by various strain of Sterptomyces.
- They have a macrolide ring structure linked to one more sugars.
- They are broad spectrum antibiotics.

Ex: Erythromycin Clarithromycin, Azithromycin.

Chemistry:

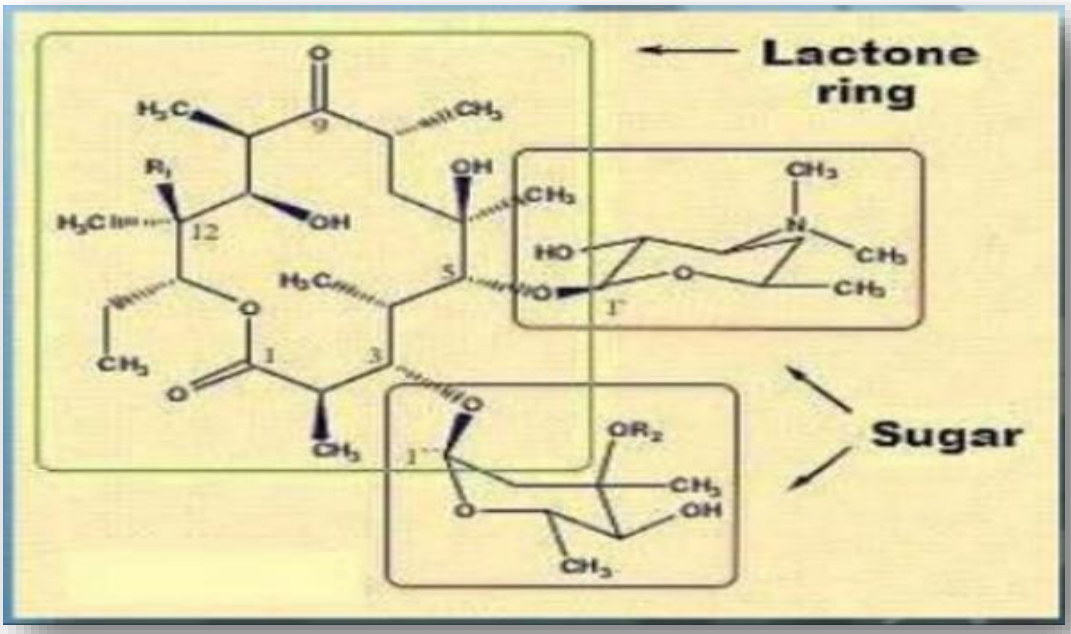
They have three common chemical characteristics.

i. A large non-planner strain less ring

ii. A ketone group

iii. A glycosidically linked amino sugar

- Usually lactone ring has 12,14 or 16 atoms in it, unsaturated with an olefinic group conjugated with the ketone function.
- They may have a neutral sugar also, in addition to the amino sugar, which is linked glycosidically to the lactone ring.



(Generalstructure of the macrolide)

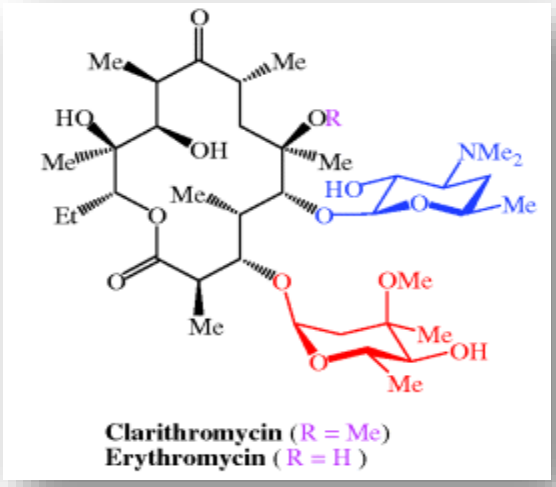
Structure activity relationship (SAR):

- As macrolide are unstable in acidic pH , a no of strategies have been utilized to improve the acidic stability of erythromycin.
- The addition of hydroxylamine to the ketone to formoxime. E.g. Roxithromycin
- Alteration of C-6 hydroxyl group: nucleophilic functionality which indicates erythromycin degradation.

- The azalides (azithromycin) are semi-synthetic 15-membered congeners in which a nitrogen atom has been introduced to expand a 14-membered precursor leads to an extended aspectrum of action.

Mechanism of action:

- Macrolides bind to 50 S subunit of the bacterial ribosome
- Inhibit polypeptide chain elongation & protein synthesis inhibition.
- Results in inhibition of growth & multiplication.



ERYTHROMYCIN:

- It is isolated from a culture of Streptomyces erythreus.
- It is a mono-acidic base, which on hydrolysis gives a basic sugar desosamine & a neutral sugar cladinose
- It is very bitter, white or yellow crystalline powder.
- It is insoluble in alcohol, but only slightly soluble in water.

Adverse effect:

- Abdominal cramps
- Epigastric distress
- Jaundice
- Transient deafness
- Hypersensitivity rashes
- Hearing impairment

Uses:

- Streptococcal pharyngitis
- Tonsillitis
- Respiratory infection
- Diphtheria
- Tetanus
- Syphilis & gonorrhoea
- Whooping cough

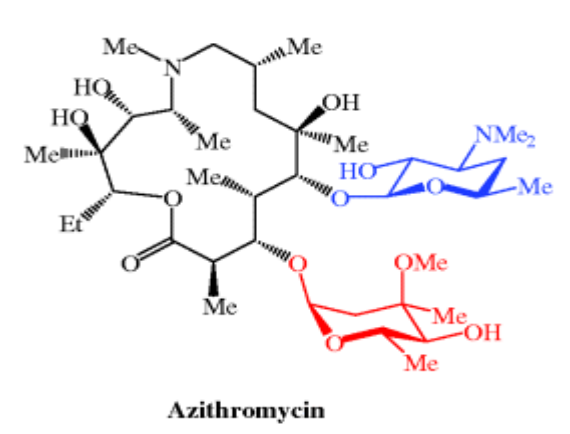
CLARITHROMYCIN:

- Chemically clarithromycin is 6-methyl ether of erythromycin.
- It is prepared by simply methylating erythromycin at 6-hydroxyl group.
- This semi-synthetic derivative fully retain the anti-bacterial activity of erythromycin with increased acid stability & oral bioavailability & reduced gastrointestinal side effect.

Adverse effect: Hearing loss, mental/mood changes, muscle weakness, eye problems (such as drooping eyelids, blurred vision), slurred speech, persistent **nausea/vomiting**, severe stomach/**abdominal pain**, dark urine, yellowing of eyes or skin.

Uses:

It is significantly more active than erythromycin against Streptococci & S.pneumoniae. but it is more expensive than erythromycin.



Azithromycin

AZITHROMYCIN:

- It is a semi-synthetic derivative of Erythromycin.
- It is a prototype of aseries of nitrogen containing, 15 member ring macrolides known as azide. It is more stable than other macrolide antibiotics.

Adverse effect:

- diarrhea or loose stools,
- nausea,
- abdominal pain,
- stomach upset,
- vomiting,
- constipation,
- dizziness,
- tiredness

Uses:

- Spectrum of anti-microbial activity is similar to erythromycin & clarithromycin.
- It is more active against gram –ve bacteria & less active against gram +ve bacteria.