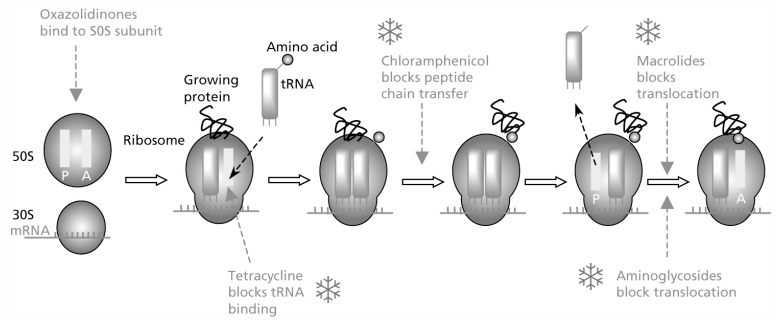
Protein Synthesis Inhibitors & Their Chemistry

Dr. Aisyah Saad
FAR241
September 2015

1

where & which

antibiotics during protein synthesis?

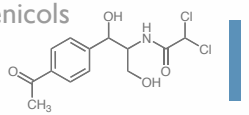


Note: Eukaryotic ribosomes consist of 60S and 40S subunits, making up 80S ribosomes

2

Protein Synthesis Inhibitors

Amphenicols



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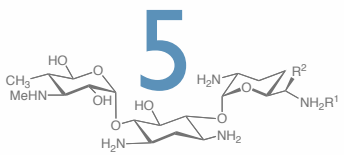

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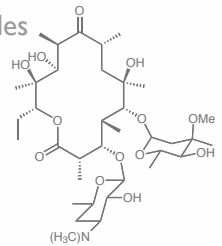
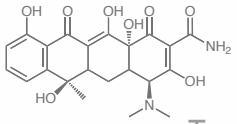
Aminoglycosides

Macrolides

2



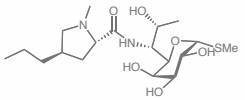


4

Tetracycline

Lincomycin

3



3

Think-Pair-Share

Which antibiotic(s) is/are NOT a glycoside?

4

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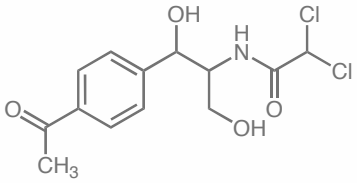
Amphenicols



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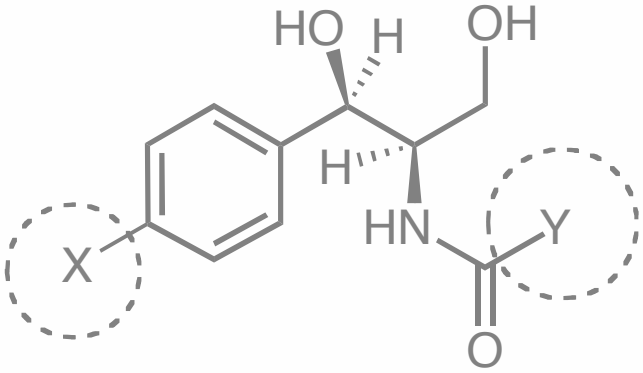
Amphenicols

a General structure



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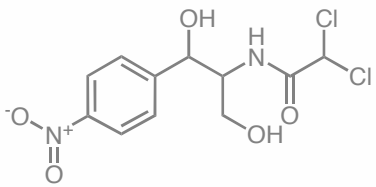
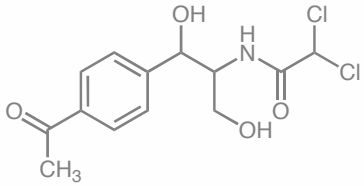
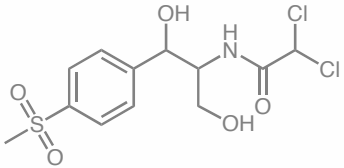
Amphenicols



chloramphenicol



cetophenicol



thiamphenicol

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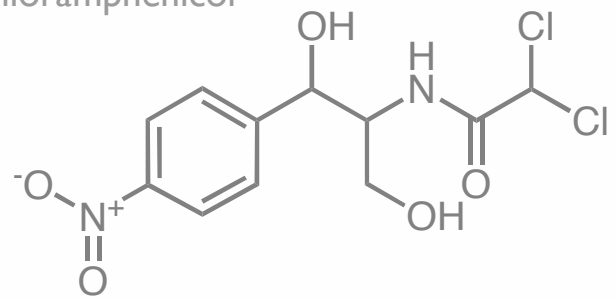
Amphenicols

Chloramphenicol



Naturally occurring compound
Four possible isomers
  Only D-threo-chloramphenicol is active (1R, 2R)
Serious adverse effect: dose-related aplastic anaemia
Thus, last resort in anti-infective therapy

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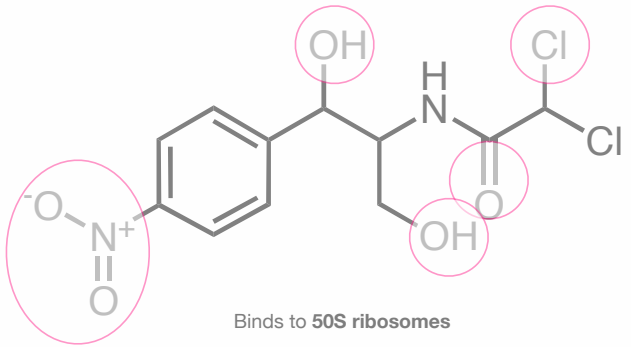
Chloramphenicol binding sites



Binds to **50S ribosomes**

Bacteriostatic

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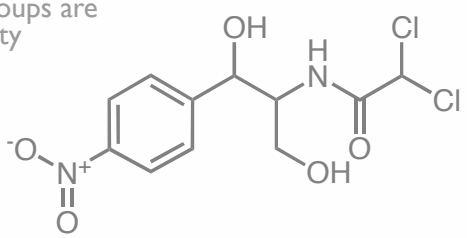
Chloramphenicol Resistance

all the functional groups are important for activity

replace nitro with other EWGs: activity drops.



but, enzyme-mediated resistance exploits this e.g.

dehydrogenation,

nitro group reduction

acetylation e.g. bacterial chloramphenicol acetyltransferases

-- acetylates the hydroxyl group

3-acetoxychloramphenicol → 1,3-diacetoxychloramphenicol

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Think-Pair-Share

Can you predict the major biotransformation pathway of chloramphenicol?

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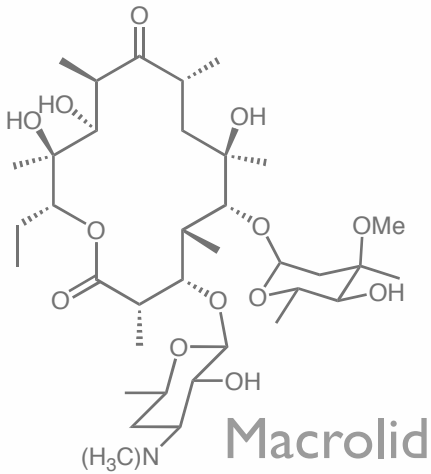
2 Macrolides



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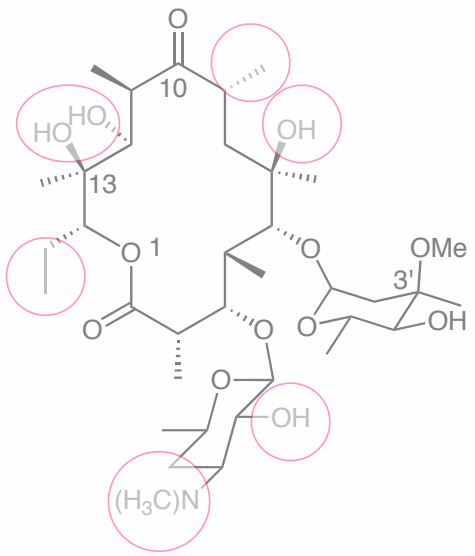
Erythromycin binding sites

Binds to **50S ribosomes**



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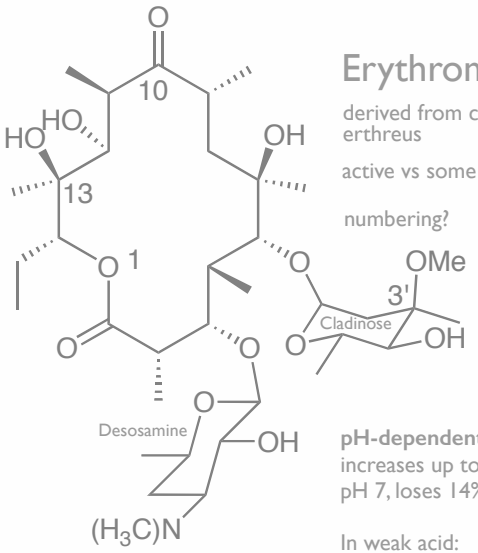
Erythromycin A

derived from certains strains of Streptomyces erthreus

active vs some G+; not Enterobacteriaceae

numbering?



Erythromycin B=no 13-OH
Erythromycin C=3'-OH

pH-dependent activity
increases up to pH 8.5 (optimum)
pH 7, loses 14% activity (after 24 hours)

In weak acid:
activity decreases (in few hours)–why??

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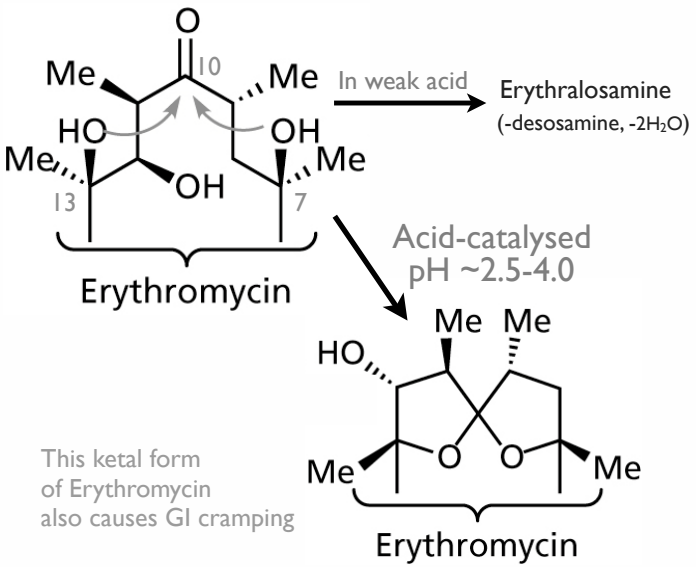
Acid Sensitivity

Clinically important reactions



This ketal form of Erythromycin also causes GI cramping

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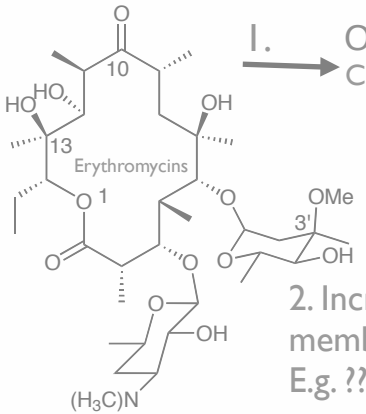
How to avoid the ketal formation ?



1. → OMe
Clarithromycin

Ketal formation is reduced thus,
1. Less cramping
2. More lipophilic, better plasma level cf Ethromycins

2. Increase ring size, up to 16-membered ring.
E.g. ??

3. ??

Macrolides

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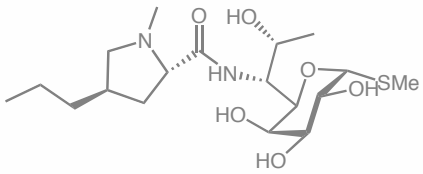

Lincomycin

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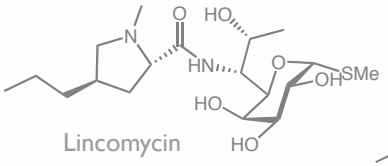
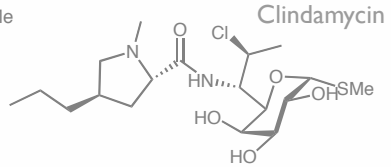
Lincomycins



Lincomycin



Clindamycin

Lincomycin is isolated from *Streptomyces lincolnesis*

Sugar component : *methyl α-thiolincosaminide (a rare 8C-sugar)*

Clindamycin : *semi-synthetic derivative*

Reserved for penicillin-resistant G+ d/t:

1. Pseudomembranous colitis (caus. *Clostridium difficile*)
2. Stevens-Johnson syndrome

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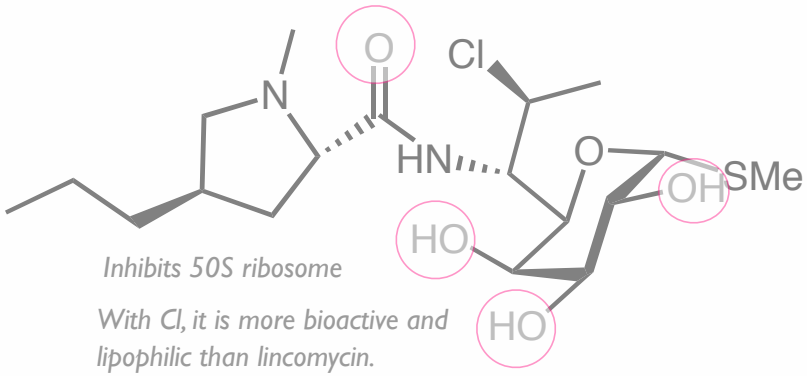
Clindamycin binding sites



Inhibits 50S ribosome

With Cl, it is more bioactive and lipophilic than lincomycin.

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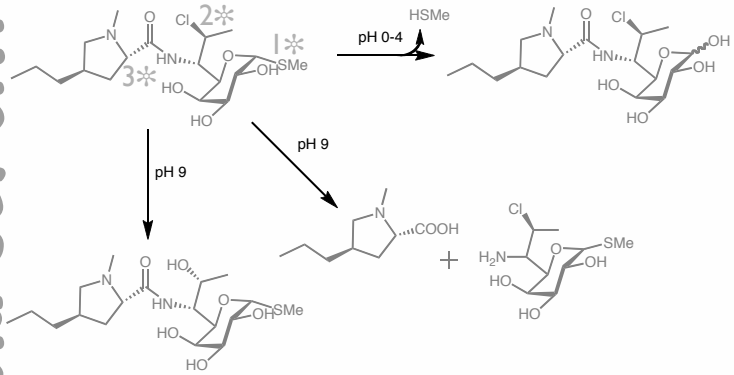
Acid Sensitivity

Clindamycin



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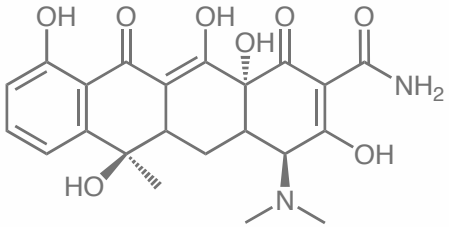
Tetracycline



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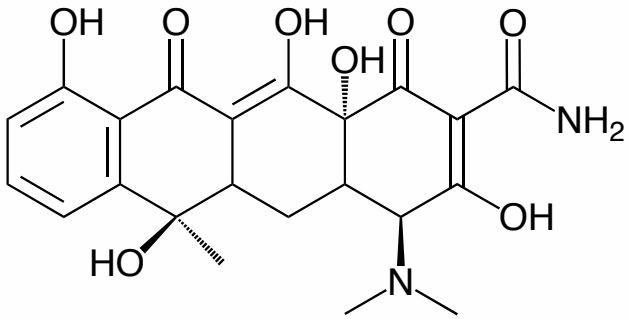
Tetracyclines



- wide spectrum of activity
- binds to **30S subunit** of **bacterial** ribosomes
- a **bacteriostatic** antibiotic

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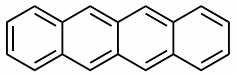
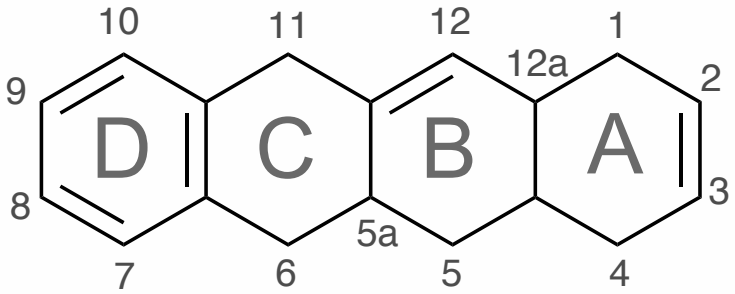


Naphthacene



1,4,4a,5,5a,6,11,12a-
octahydronaphthacene

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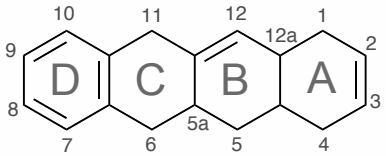
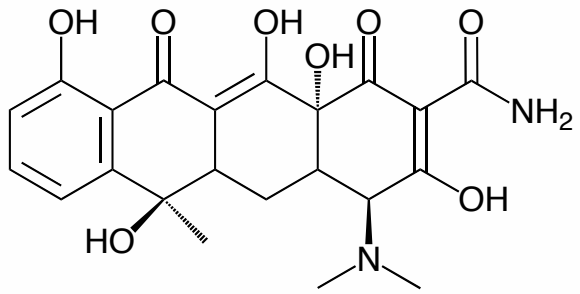


Tetracycline



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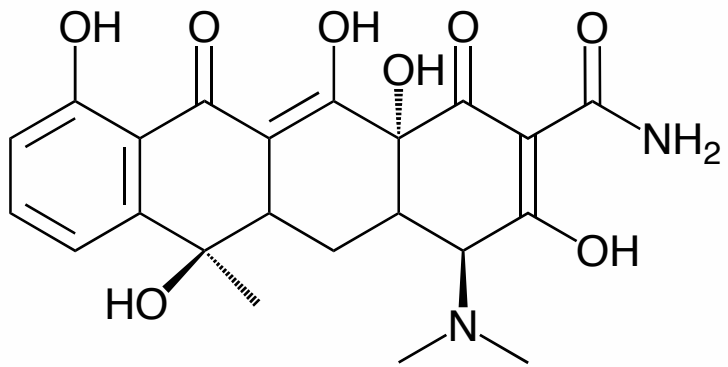
Tetracyclines Chemistry



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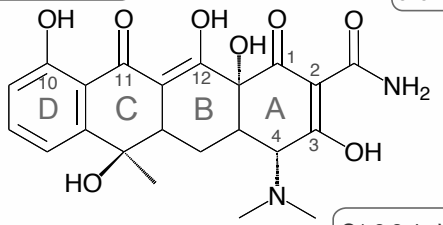
Tetracyclines

Amphoteric in nature.
Has 3 pKa values at different parts of its structure

A trivalent acid.
Low aqueous stability.
Epimerizes and chelates readily.

C1-12a : α-ketol group with a tertiary carbinol function - blocks enolization



B-C-D rings : a chromophore consisting a phenol and β-diketone structure. Visually yellow.
Ring A : another chromophore
Sensitive to light : due to A & BCD

C1,2,3,4 : Vinylogous α-amino ketone group; the dimethylamino group can be easily liberated

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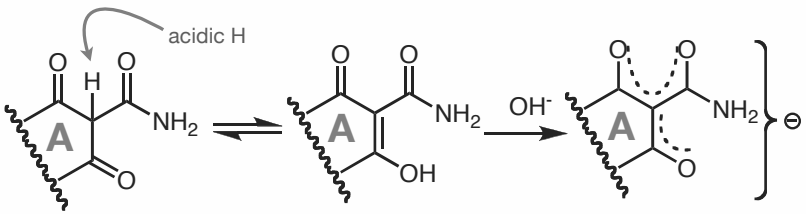
Tetracyclines

Tricarbonyl Framework



Tetracycline shows acidic nature with pK_{a1} = 2.8 - 3.4
where enolization in Ring A tends to take place.

Guide to pK_a
HBr, pK_a = -9.0; Acetic acid, 4.76; Water, 15.7, CH_3, 50

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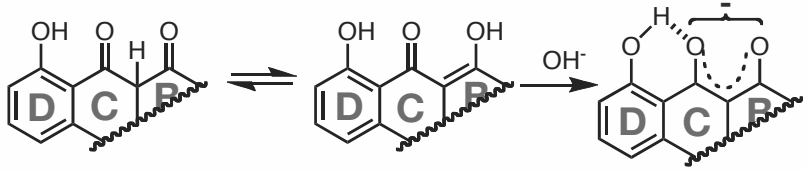
Tetracyclines

β-dicarbonyl system

"Phenolic enone system"



Almost neutral pK_a = 7.2 - 7.8
where enolization in Ring BCD occurs

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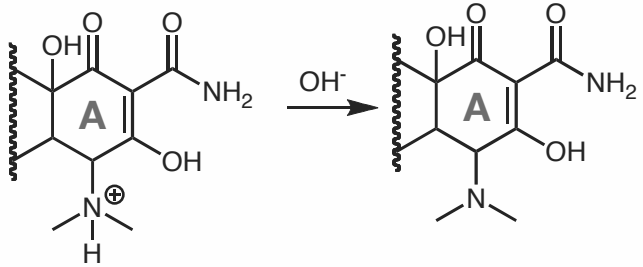
Tetracyclines



pK_a = 9.2 - 9.7

Tetracycline is amphoteric. It is sold as Na or Cl salts.

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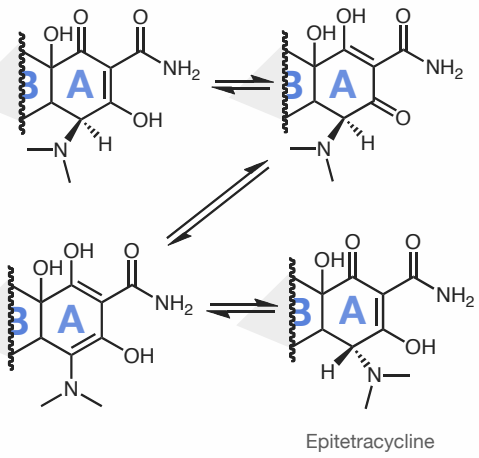
Tetracyclines

Epimerization



Epitetracycline

Extremely important

- occurs between pH 2 - 6
- favoured in buffered solutions, which leads to an equilibrium consisting 2/3 tetracycline & 1/3 epitetracycline
- Epitetracycline is 1.5% of tetracycline
- Take **extra, extra care** when you're asked to prepare an solution of tetracycline

***Chemistry important to formulation**

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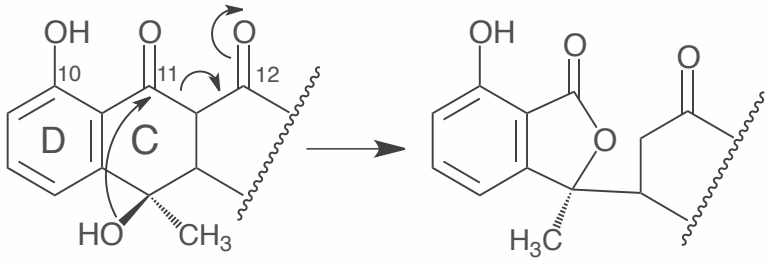
Tetracyclines

Under basic conditions:



isotetracycline

***Chemistry important to formulation**

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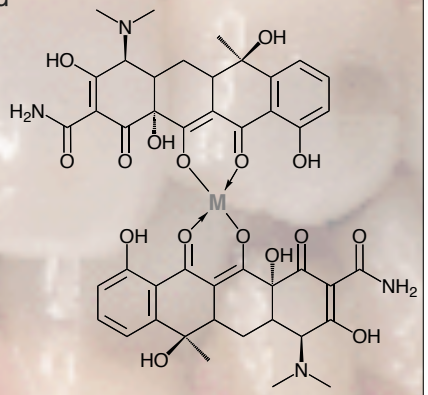
Chelation with Di- & Trivalent Metal ions: the complex formed

Are not active, and not absorbed from GIT



***Clinically important chemistry**

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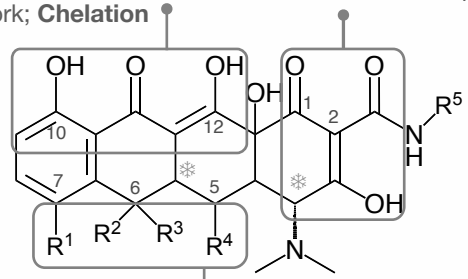
Tetracyclines

Summary

Phenolic enone system
The principal functional framework; **Chelation**

Trione framework. Weak acid; involves in epimerization



Changes on these substituents have little detrimental effects on activity

❄ C4 & C5a must maintain the right configuration
Chelation

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05

Aminoglycosides

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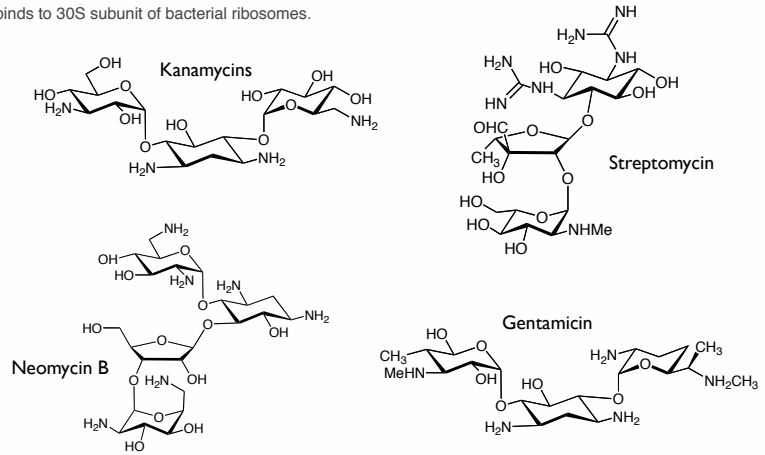
sourced from strains of *Streptomyces* and *Micromonospora*.

binds to 30S subunit of bacterial ribosomes.

family



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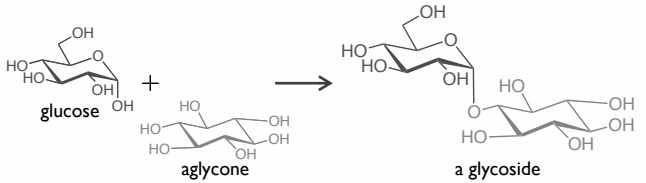
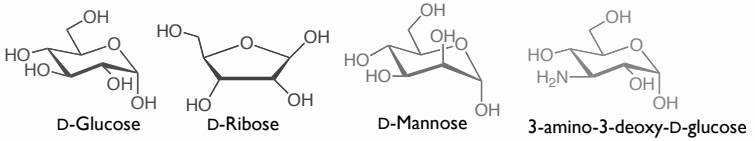
- Terminology
  - A glycoside is...



- Some medicinally-important monosaccharides



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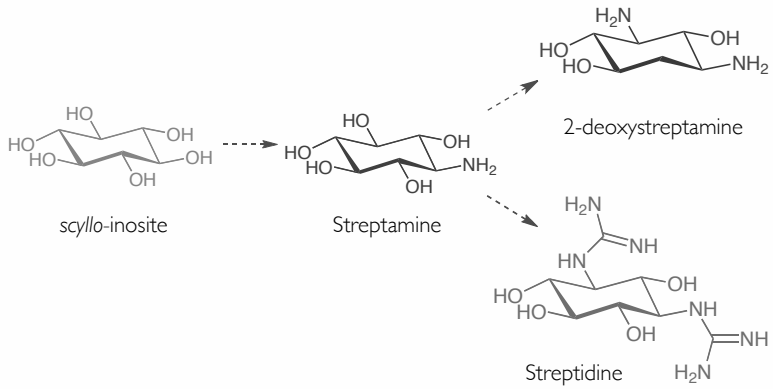
Amino alcohol of Aminoglycosides(Aglycones)



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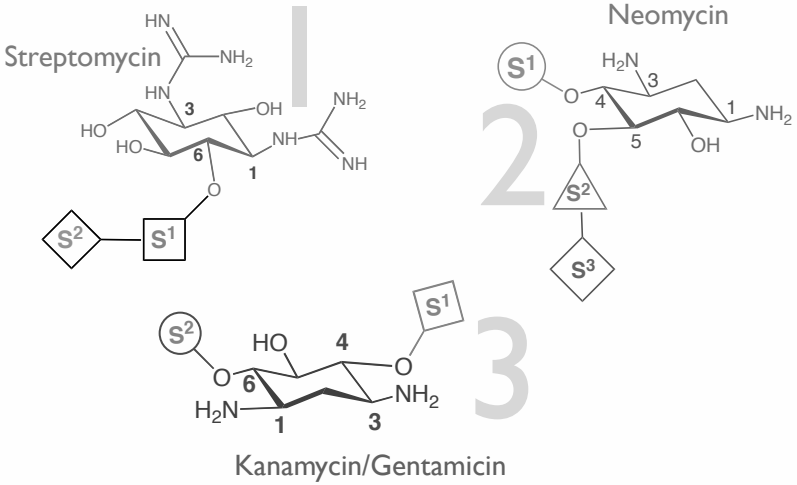

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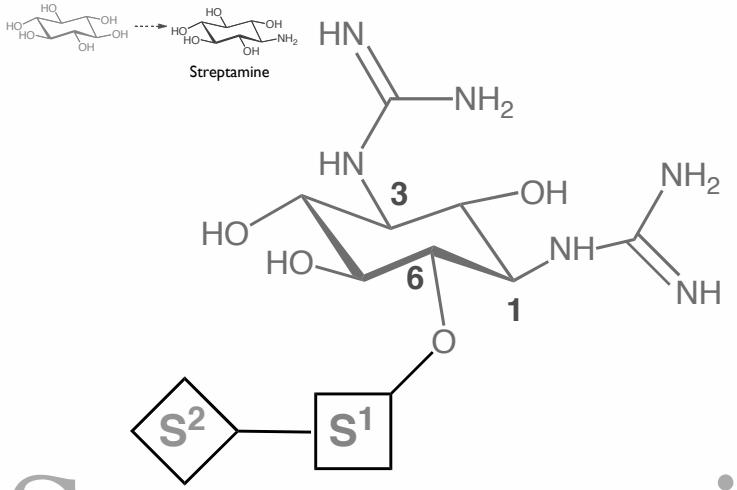

Streptomycin

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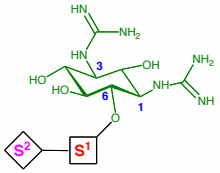
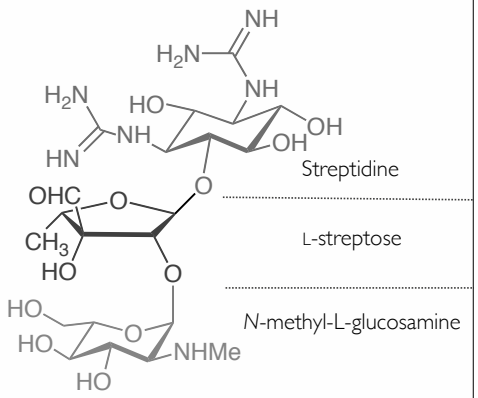


- the nucleus streptidine is linked to other sugars
- a front-line drug against M. tuberculosis in combination with other drugs
- exhibits ototoxicity
- rapid resistance



Streptomycin

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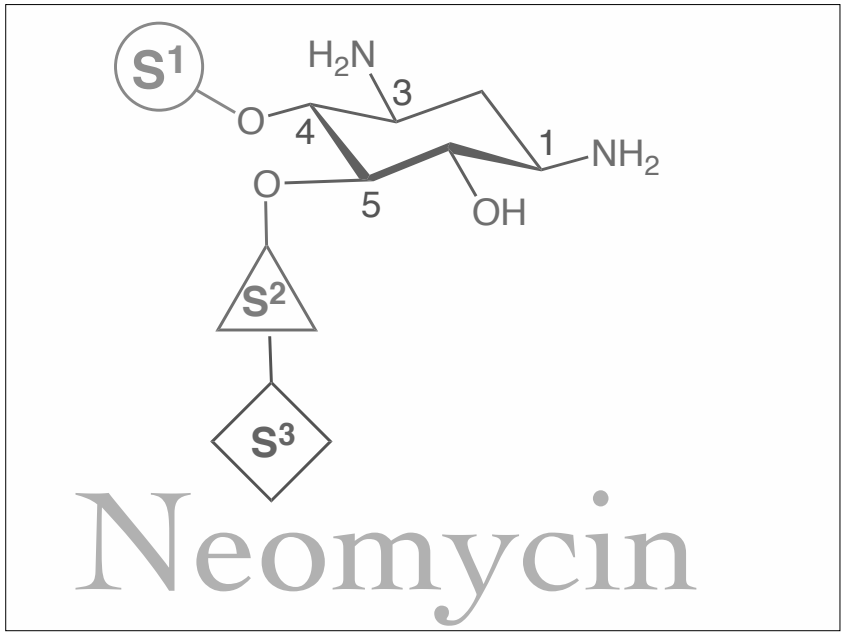

Neomycin

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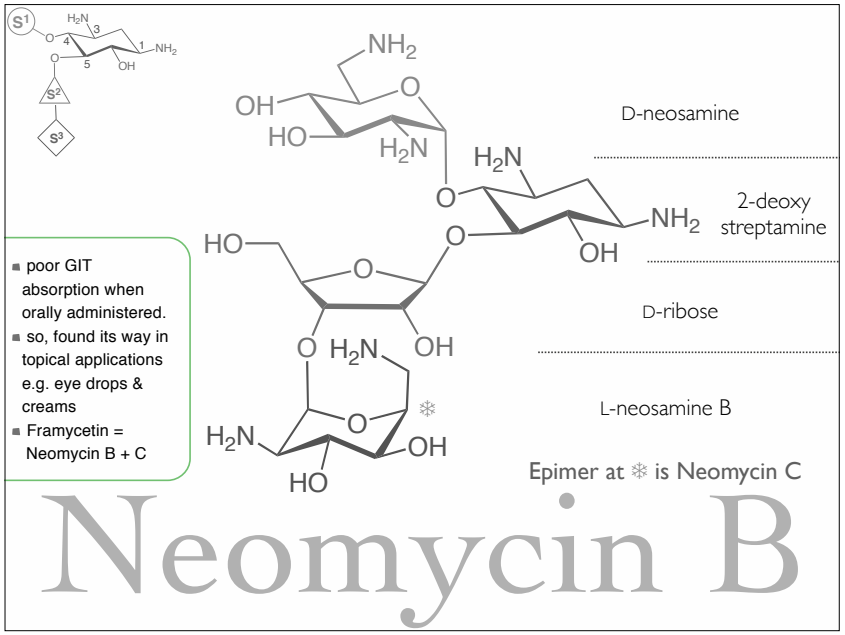

- poor GIT absorption when orally administered.
- so, found its way in topical applications e.g. eye drops & creams
- Framycetin = Neomycin B + C

Neomycin B

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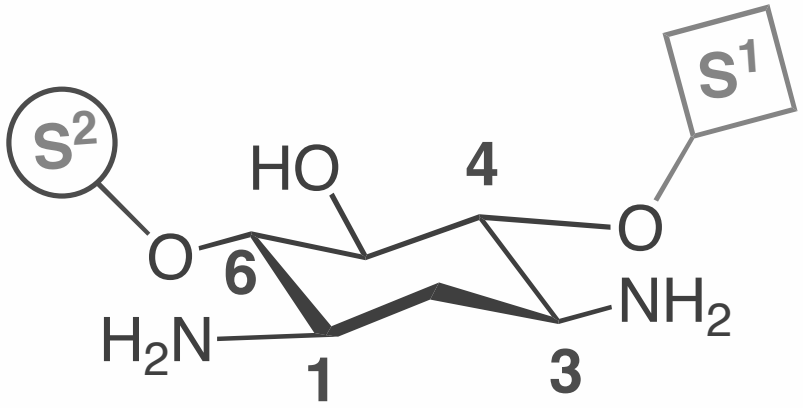
Kanamycin/Gentamicin



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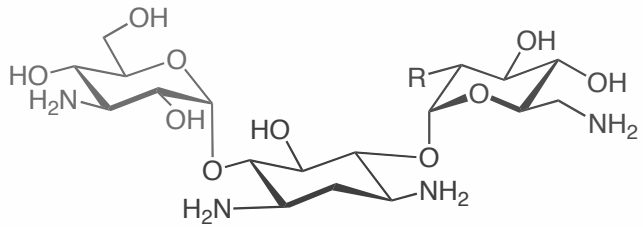
Kanamycin

- a complex of three antibiotics i.e. Kanamycin A, B & C.
- potent against Gram +ve (including penicillin-resistant streptococci) & Gram -ve bacteria.
- a second-line drug in tuberculosis treatment.



3-amino-3-deoxy-D-glucose | 2-deoxystreptamine | 6-amino-6-deoxy-D-glucose

Kanamycin A: R = OH
Kanamycin B: R = NH_2

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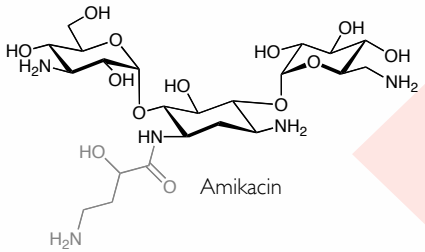
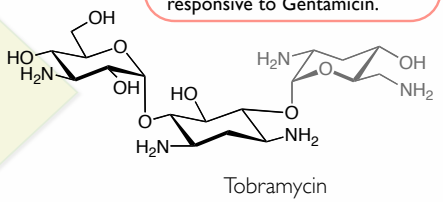
Kanamycin

Analogues of



- Inactivating enzymes catalyse biochemical reactions e.g. *O*-phosphorylations, *O*-adenylation, *N*-acylation
- Stability towards inactivating enzymes is conferred by the 4-amino-2-hydroxybutyl group
- Treatment of serious Gram -ve infections which are not responsive to Gentamicin.

- Also called 'Nebramycin Factor 6'
- Less susceptible to enzymatic degradation due to the lack of 3-OH of the 2-amino sugar
- Slightly more active towards Ps. aeruginosa than Gentamicin



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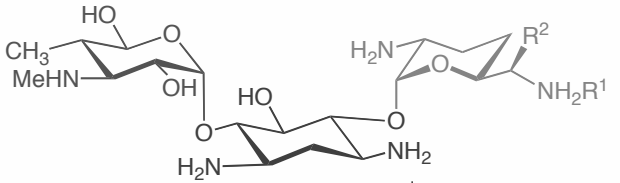
Gentamicin

- isolated from *Micromonospora purpurea*
- a mixture of three components i.e. Gentamicin C_1, $C_{1\alpha}$ & C_2
- active against Gram +ve & -ve plus some *Ps. aeruginosa* strains
- co-administered with carbenicillin to delay onset of resistance



L-garosamine | 2-deoxystreptamine | D-purpurosamine

Gentamicin C_1 ; $R^1 = CH_3$ $R^2 = CH_3$
Gentamicin $C_{1\alpha}$; $R^1 = H$, $R^2 = H$
Gentamicin C_2 ; $R^1 = CH_3$, $R^2 = H$

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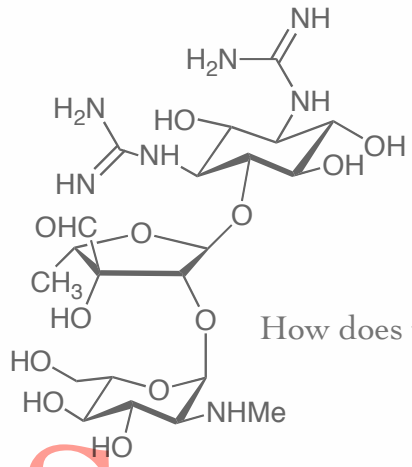

How do they look like?

How does their structures affect how they work/act?

Summary

Aminoglycosides

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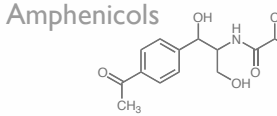
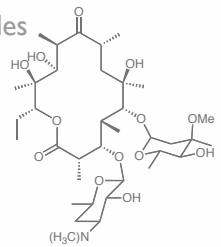


1

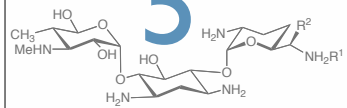
Amphenicols



2

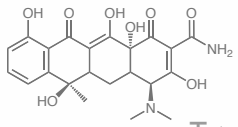
Macrolides

5



Aminoglycosides

Chemistry
Protein Synthesis Inhibitors

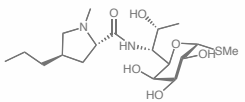


4

Tetracycline

3

Lincomycin



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