

Antibacterial Agents

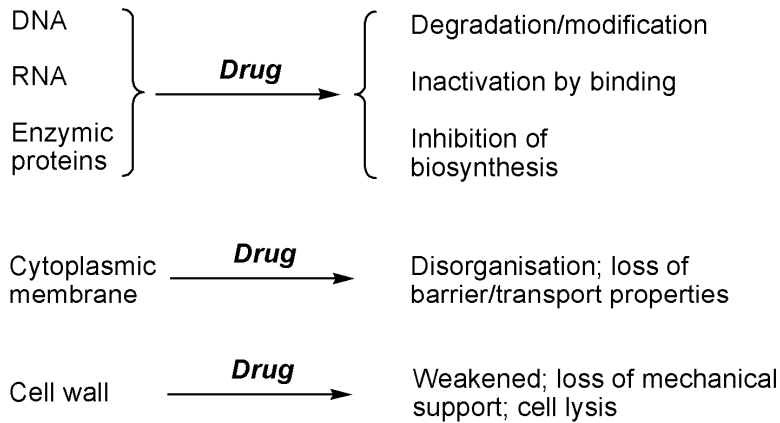
Lecture 3

Overview of coverage

This lecture provided gives a **broad overview** of the diversity of **antibacterial agents** with selected reference to:

- **chemical structure**: mainly restricted to general features
- **origins**: natural sources; some chemical syntheses
- **applications**: topical or systemic use etc.
- **antimicrobial spectrum**: some illustrations only
- **type of action**: bactericidal vs. bacteriostatic (inhibitory)
- **site and mode of action**: the 'where and how / why' a drug works
- **resistance**: mechanisms; causes; cures? (Lecture 5)

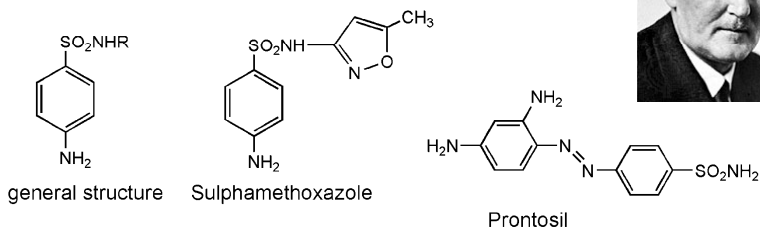
Antimicrobial Drug Action



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Antimetabolites

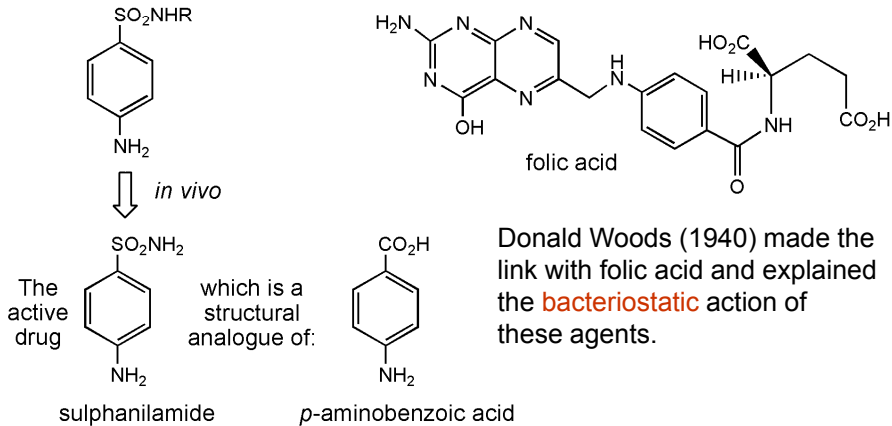
- Antimetabolites are mostly analogues of key “growth factors” such as folic acid (folate) analogues, nucleic acids etc.
- Prontosil, a sulphonamide, was the first **fully synthetic antibacterial agent** discovered in the 1930s by Gerhard Domagk. (Nobel Prize 1939, photo c. 1960).



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Sulphonamides

- Sulphonamides are metabolised *in vivo* to sulphanilamide



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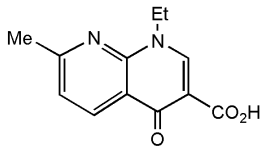
Cell membrane disruptors

- Most are cationic polypeptides (which have an excess of basic side chain functional groups over acidic side chains)
- E.g. tyrocidin, gramicidin S, bacitracin, **polymyxins produced by spore-forming GPB (*Bacillus* spp.)**. (cf nisin)
- Various structural types are found
 - Cyclic or linear
 - some with ester linkages also
 - some with fatty acyl groups
 - D-amino acids commonly present.
- In most cases these agents are **bactericidal**
- Cause **disruption of the structure or function of the bacterial membranes** (permeability barrier).
- Little systemic use because of **toxic side-effects**

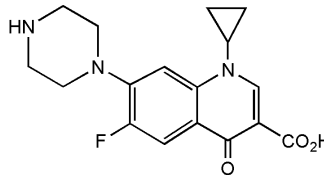
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Inhibitors of nucleic acid structure or function

- **Quinolones**: prototype drug was nalidixic acid (1962): active against Gram-negative bacteria.
- Nalidixic acid used for urinary tract infections but resistance developed quickly.



Nalidixic acid



Ciprofloxacin

- Quinolones inhibit **DNA gyrase** (topoisomerase II), an enzyme involved in uncoiling super coiled DNA
- These have selective action on prokaryotes unlike many other drugs acting on DNA.

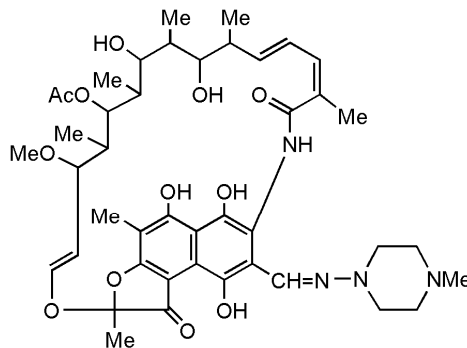
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Inhibitors of nucleic acid structure or function

- The **ansamycins** are two groups of macrocycles, the **rifamycins** and **streptovaricins**, incorporating aromatic residues.

- Rifampin is a semi-synthetic ansamycin and still a major TB drug.

- Inhibit mRNA biosynthesis;
bactericidal action



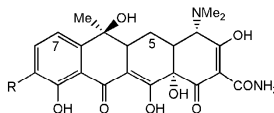
Rifampicin (rifampin)

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Protein Synthesis Inhibitors

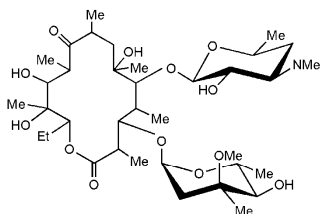
- Tetracyclines (1948→)

e.g. **doxycycline**
prevents binding of
aminoacyl t-RNA to
the ribosomes



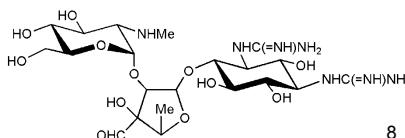
- Macrolides (1952→)

e.g. **ethryromycin**
causes premature release
of incomplete peptide from
ribosome still attached to t-RNA



- Aminoglycosides (1943→)

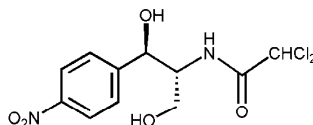
e.g. **streptomycin**
complex action at
multiple sites



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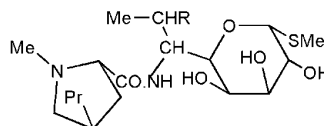
Protein Synthesis Inhibitors

- Chloramphenicol (1950→)



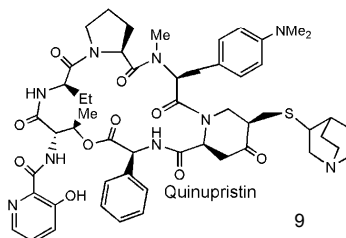
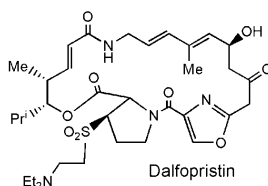
- Lincosamides (1963→)

e.g. clindamycin (R=OH)
and lincomycin (R=Cl)



- Streptogramins
(1961→)

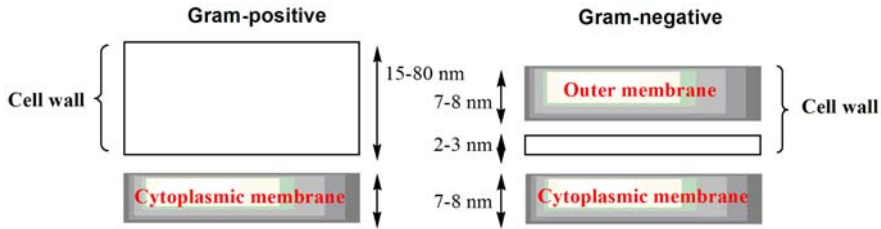
e.g. quinupristin
and dalfopristin



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Cell Wall Biosynthesis Inhibitors

- **Reminder:** the **cell wall** is not present in mammalian cells so presents a unique target for antibacterial action.



- **Peptidoglycan**, a biopolymer made up of saccharide and peptidic components, is a major constituent of the cell wall.
- Main classes of cell wall inhibitors are the **β -lactams** and the **glycopeptides** which **inhibit the biosynthesis of peptidoglycan**.

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β -Lactams

- All examples contain the 4-membered lactam ring; a strained, cyclic amide which is key to its biological activity. E.g. the penicillins.

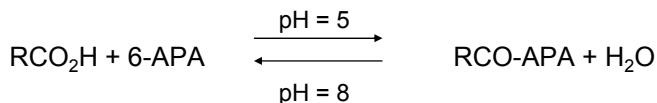


- they are bactericidal **only against growing cells** otherwise bacteriostatic
- they are inherently unstable towards acid due to the strained four-membered ring
- many are now unstable with regard to enzymic inactivation

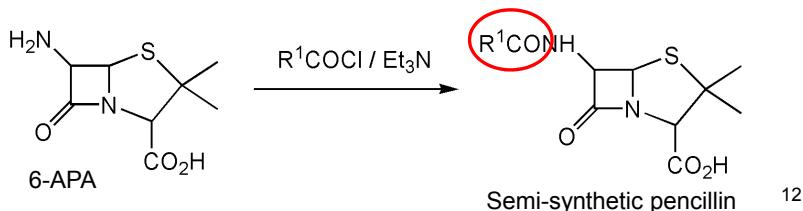
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Semi synthetic penicillins

- Beechams discovered an enzymic method to deacylate penicillins to 6-aminopenicillanic acid (6-APA) without breaking the lactam ring:



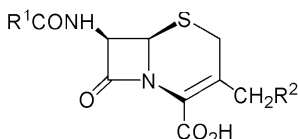
- Simple acylation chemistry with an acid chloride or anhydride yielded many semi-synthetic variants such as methicillin



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Cephalosporins

- 'Ceph's' are 4,6 bicyclic analogues (cephems) of the penicillins

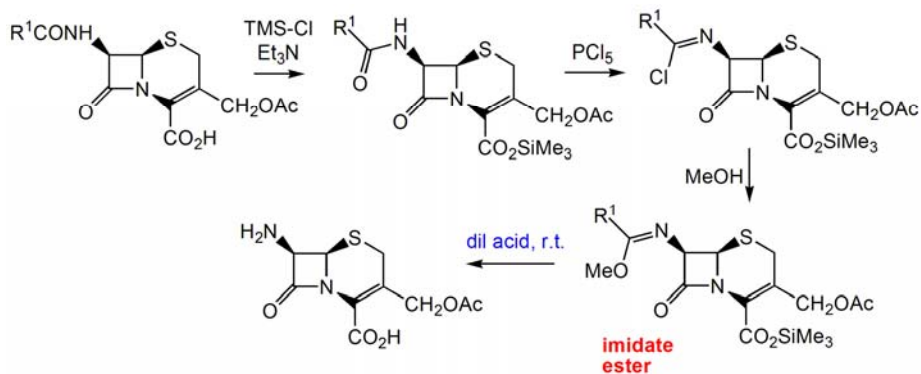


- Biological activity poor relative to "pens", but improved
 - resistance to acid
 - resistance to β -lactamase enzymes
 - have a broader spectrum of activity
- Variants cannot be obtained by adding acids to the fermentation broths and 7-ACA cannot be produced enzymically!
- How can semi synthetic variants be made on large scale?

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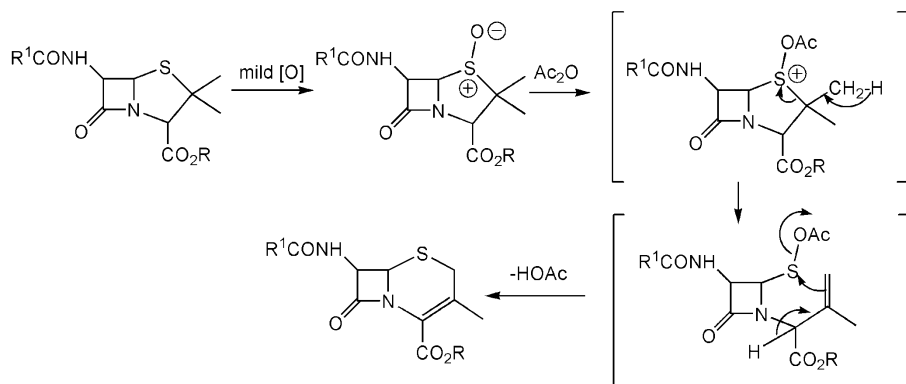
Cephalosporins

- need a chemical method to hydrolyse the exocyclic amide (but not the more reactive β -lactam??)



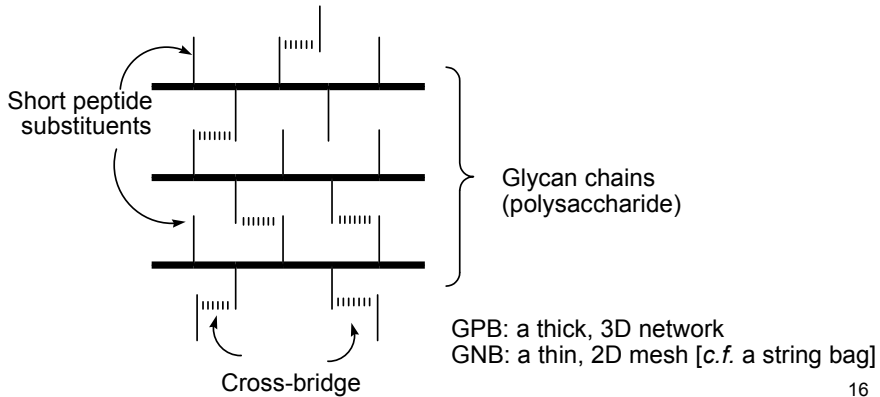
Cephalosporins

- “Cephs” can be made from the more readily available penicillins *via* a Pummerer rearrangement.



Mode of action of β -lactams

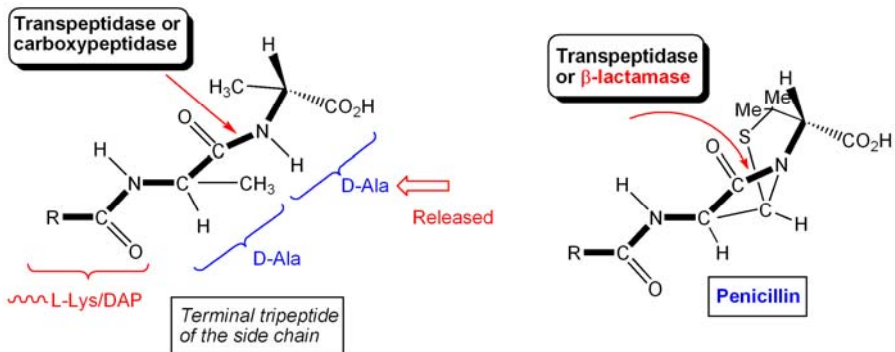
- **Reminder:** Late-stage peptidoglycan biosynthesis involves the formation of inter-strand, peptide cross-links between neighbouring glycan (polysaccharide) chains.



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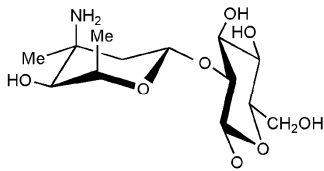
Strominger hypothesis

- Penicillins irreversibly bind to (deactivate) the transpeptidase enzymes so stopping the process of peptidoglycan cross linking.

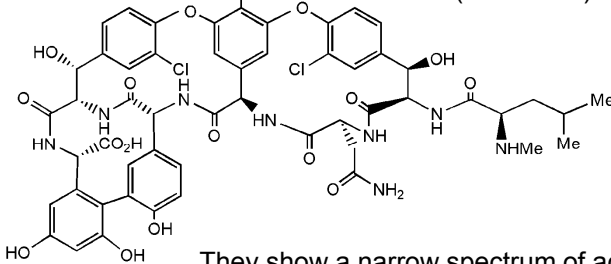


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Glycopeptides



Glycopeptides are very large, complex, polycyclic antibiotics incorporating amino acids and sugars, with other functions, Examples include **vancomycin** (shown left) and **teicoplanin**.

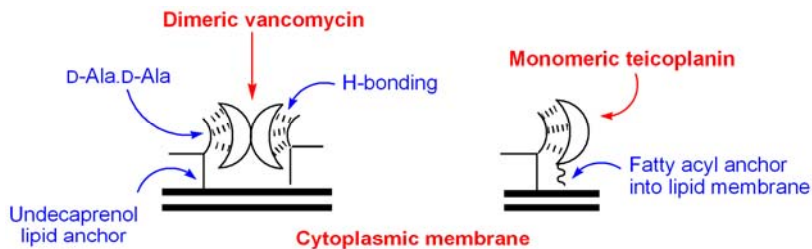


They show a narrow spectrum of activities, but last line of defence (?) against some important or **multidrug-resistant GPB**. [GPB **only** as too large to penetrate GNB]

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Glycopeptides: mode of action

The glycopeptide antibiotics (most notably **vancomycin** but also **teicoplanin**) inhibit late stages of peptidoglycan synthesis involving transfer of completed, lipid-bound precursor units from the cytoplasmic membrane to the growing cell wall



High-affinity binding of glycopeptides *via* the "chelate effect"

Inhibition occurs through **five H-bonds** to the terminal dipeptide D-Ala-D-Ala of the peptide side chains of disaccharide "monomers" **before** they are incorporated into the growing glycan chains. Interaction is also facilitated by **dimerisation** (*vancomycin*) or the presence of a **lipid anchor** (*teicoplanin*).

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