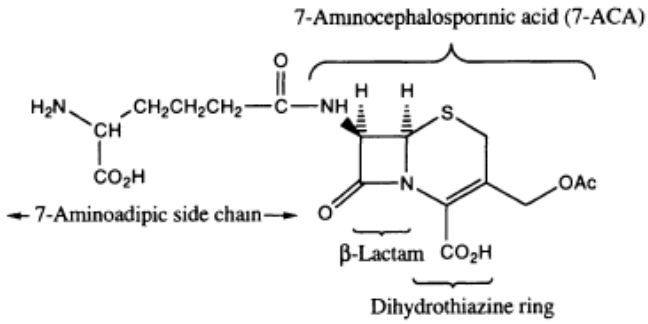
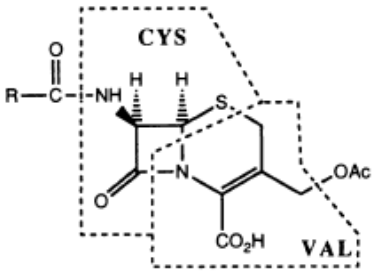
Cephalosporins

Cephalosporin C has been used in the treatment of **urinary tract infections** since it is found to concentrate in the urine and survive the body's hydrolytic enzymes.

A chlorine atom is now introduced to form an **amino chloride** which can then be to hydrolysis than the β-lactam ring and so treatment with aqueous acid successfully gives the desired 7-ACA which can then be acylated to give a range of analogues.



Cephalosporin C.



Cephalosporin skeleton.

The most commonly used of these cephalosporin analogues is **Cephalothin**. Cephalothin is (1)Resistant to penicillinase from *Staph. aureus* infections and (2)Poorly absorbed in the gastrointestinal tract and has to be injected. In addition to (3)Less chance of allergic reactions and can be used for patients with allergies to penicillin.

Another example is **Cephaloridine** which contains a **pyridinium** group in place of the **acetoxy** group. It is characterized by (1)Soluble in water because of the positive charge, (2)Low serum protein binding leads to good levels of free drug in the circulation, (3)Some kidney toxicity at high doses, and (4)Poorly absorbed through gut wall and has to be injected.

A second example is **cephalexin** which has no substitution at position 3. This is one of the few cephalosporins **which is absorbed through the gut wall and can be taken orally**.

Synthesis of 3-methylated cephalosporins

The synthesis of 3-methylated cephalosporins from cephalosporins is very difficult and it is easier to start from the penicillin nucleus. The synthesis involves a ring expansion, where the five-membered thiazolidine ring in penicillin is converted to the six-membered dihydrothiazine ring in cephalosporin.

The only substitution which has been useful at position 7 has been the introduction of the 7-alpha-methoxy group to give a class of compounds known as the **cephamycins**.

Second-and third-generation cephalosporins-oximinocephalosporins

Research is continually being carried out to try and discover cephalosporins with an improved spectrum of activity or which are active against particularly resistant bacteria.

One group of cephalosporins which has resulted from this effort has been the **oximinocephalosporins**.

The first useful agent in this class of compounds was **cefuroxime** (**Glaxo**) which **has good resistance to β-lactamases and mammalian esterases**. The drug is very safe, has a wide spectrum of activity, and is useful against organisms which have become resistant to penicillin. However, it is not active against 'difficult' bacteria such as *Pseudomonas aeruginosa* and it also has to be injected.

Novel β-lactam antibiotics

Although penicillins and cephalosporins are the best known and most researched β-lactams, there are other β-lactam structures which are of great interest in the antibacterial field.

Clavulanic acid

It has **weak** and unimportant antibiotic activity. However, it is a powerful and irreversible inhibitor of most β-lactamases and as such is now used in combination with traditional penicillins such as **amoxicillin**.

Thienamycin

It is potent with an extraordinarily broad range of activity against Gram-positive and Gram-negative bacteria (including *P. aeruginosa*). It has low toxicity and shows a high resistance to β-lactamases. This resistance has been ascribed **to the presence of the hydroxyethyl side chain.**

However, it shows poor metabolic and chemical stability, and is not absorbed from the gastrointestinal tract. Therefore, analogues with increased chemical stability and oral activity would be useful.

Olivanic acids

They have **very strong β-lactamase activity**, in some cases 1000 times more potent than clavulanic acid. They are also effective against the β-lactamases which can break down cephalosporins. These β-lactamases are unaffected by clavulanic acid.

Nocardicins

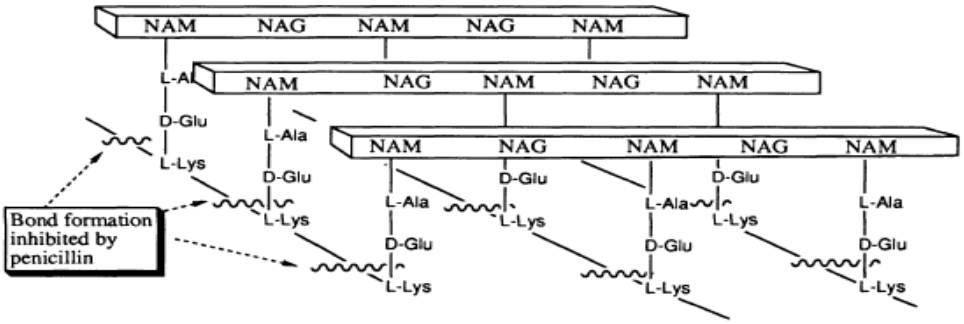
However, it is surprising that they should show any activity at all since they contain a single β-lactam ring unfused to any other ring system. The presence of a fused second ring has always been thought to be essential in order to strain the β-lactam ring sufficiently for antibacterial activity.

One explanation for the surprising activity of the nocardicins is that they operate via a different mechanism from penicillins and cephalosporins. There is some evidence supporting this in that the nocardicins are inactive against Gram-positive bacteria and generally show a different spectrum of activity from the other β-lactam antibiotics.

It is possible that these compounds act on cell wall synthesis by inhibiting a different enzyme. They also show low levels of toxicity.

The mechanism of action of penicillins and cephalosporins

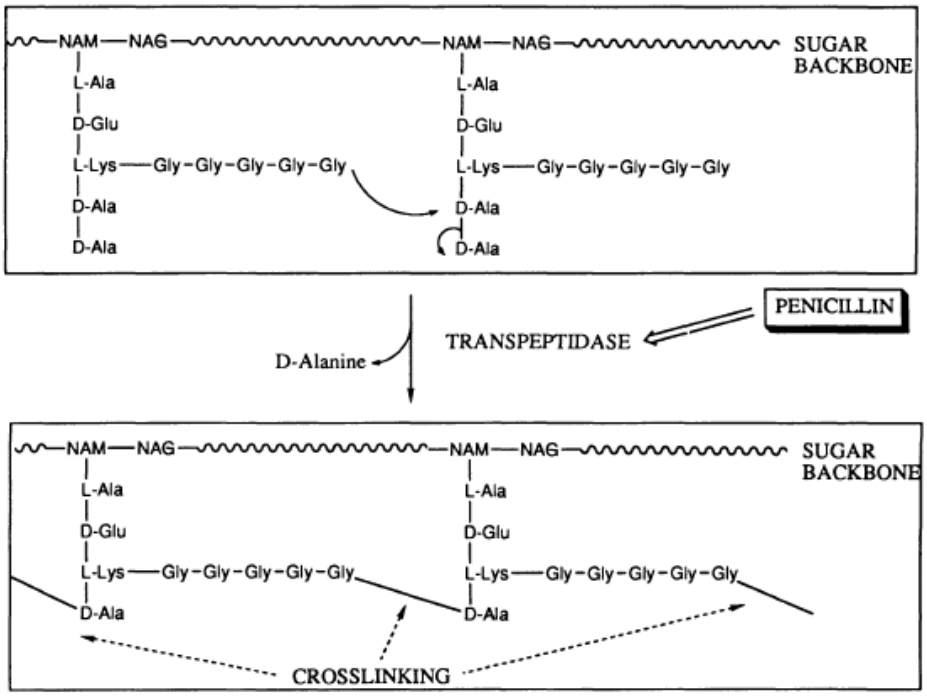
The wall is a peptidoglycan structure. In other words, it is made up of peptide units and sugar units. The structure of the wall consists of a parallel series of sugar backbones containing two types of sugar (*N*-acetyl muramic acid (**NAM**) and *N*-acetyl glucosamine (**NAG**)). Peptide chains are bound to the NAM sugars, and in the final step of cell wall biosynthesis, these peptide chains are linked together by the displacement of D-alanine from one chain by glycine in another.



Peptidoglycan structure.

It is this final cross-linking reaction which is inhibited by penicillins and cephalosporins, such that the cell wall framework is not meshed together. As a result, the wall becomes 'leaky'. Since the salt concentrations inside the cell are greater than those outside the cell, water enters the cell, the cell swells, and eventually lyses (bursts).

The enzyme responsible for the cross-linking reaction is known as the **transpeptidase** enzyme.



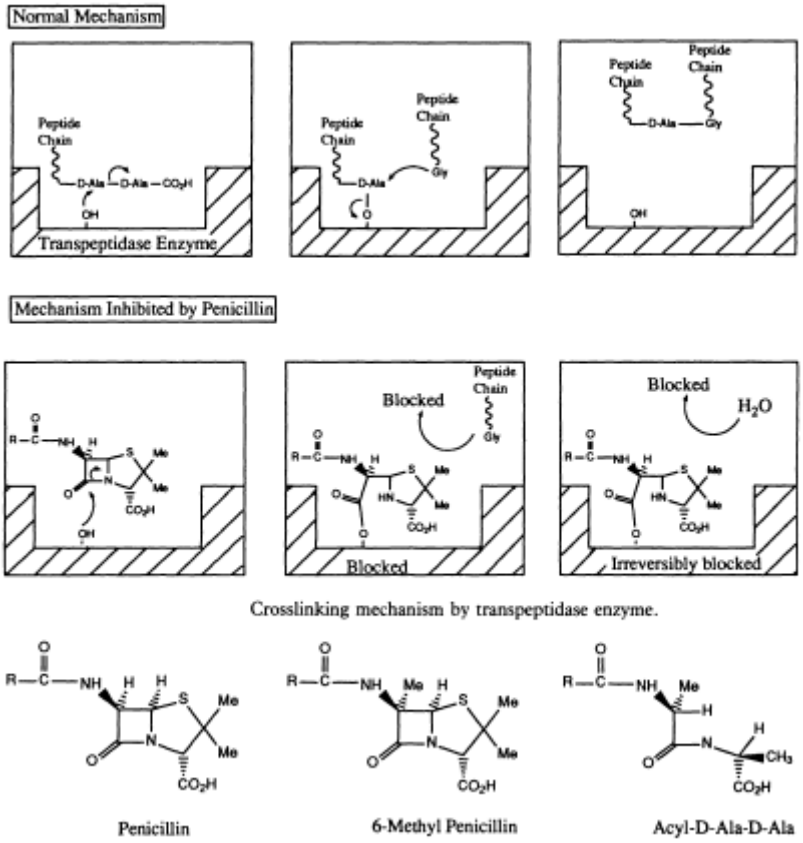
Crosslinking of bacteria cell walls inhibited by penicillin.

It has been proposed that penicillin has a conformation which is similar to the transition-state conformation taken up by D-Ala-D-Ala-the portion of the amino acid chain involved in the cross-linking reaction. Since this is the reaction centre for the transpeptidase enzyme, it is quite an attractive theory to postulate that the enzyme mistakes the penicillin molecule for the D-Ala-D-Ala moiety and accepts the penicillin into its active site. **Once penicillin is in the active site, the normal enzymatic reaction would be carried out on the penicillin**.

In the normal mechanism, the amide bond between the two alanine units on the peptide chain is split. The terminal alanine departs the active site, leaving the peptide chain bound to the active site. The terminal glycine of the pentaglycyl chain can then enter the active site and form a peptide bond to the alanine group and thus remove it from the active site.

The enzyme can attack the β-lactam ring of penicillin and open it in the same way as it did with the amide bond. However, penicillin is cyclic and as a result the molecule is not split in two and nothing leaves the

active site. Subsequent hydrolysis of the acyl group does not take place, presumably because glycine is unable to reach the site due to the bulkiness of the penicillin molecule.



However, there is some doubt over this theory since there are one or two anomalies. For example, 6-methylpenicillin is a closer analogue to D-Ala-D-Ala. It should fit the active site better and have higher activity. On the contrary, it is found to have lower activity.

An alternative proposition is that penicillin does not bind to the active site itself, but binds instead to a site nearby. By doing so, the penicillin structure overlaps the active site and prevents access to the normal reagents - the umbrella effect. If a nucleophilic group (not necessarily in the active site) attacks the β-lactam ring, the penicillin becomes bound irreversibly, permanently blocking the active site.