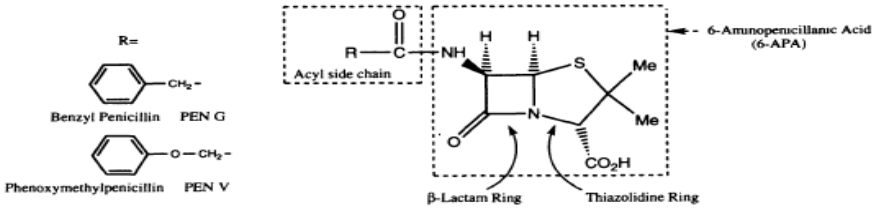
Antibacterial agents which inhibit cell wall synthesis

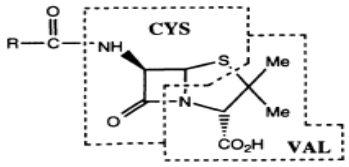
There are two major classes penicillins and cephalosporins.

Penicillins

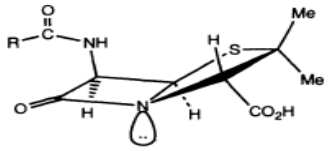
Penicillin contains a highly unstable-looking bicyclic system consisting of a four membered (**β-lactam ring**) fused to a five-membered **thiazolidine ring**.



The structure of penicillin.



Penicillin appears to be derived from cysteine and valine.



Shape of penicillin.

Properties of penicillin G (the first penicillin to be isolated)

1- Active versus Gram-positive bacilli (e.g. *staphylococci*, *meningitis*, and *gonorrhoea*) and many (but not all) Gram-negative cocci.

2- Non-toxic**:** penicillins are amongst the safest drugs known to medicine.

3- Not active over a wide range (or spectrum) of bacteria.

4- Ineffective when taken **orally** since it breaks down in the acid conditions of the stomach. Penicillin G can only be administered by **injection**.

5- Sensitive to all known (***β*-lactamases**). These are enzymes produced by penicillin resistant bacteria which catalyze the degradation of penicillins.

6- Allergic reactions are suffered by some individuals.

Clearly, there are several problems associated with the use of penicillin G :

A. The acid sensitivity of penicillins

There are three reasons for the acid sensitivity of penicillin G :

1-Ring strain.

The bicyclic system in penicillin consists of a four-membered ring and a five membered ring. As a result, penicillin suffers large angle and torsional strains. Acid-catalyzed ring opening relieves these strains by breaking open the more highly strained four-membered lactam ring.

Ring opening.

2-A highly reactive (β-lactam carbonyl group).

The carbonyl group in the (β -lactam ring) is highly susceptible to nucleophiles and as such does not behave like a normal tertiary amide which is usually quite resistant to nucleophilic attack. This difference in reactivity is due mainly to the fact that stabilization of the carbonyl is possible in the tertiary amide, but impossible in the (β -lactam ring).

3-Influence of the acyl side-chain (neighboring group participation).

The neighboring acyl group can actively participate in a mechanism to open up the lactam ring. Thus, penicillin G has a self-destruct mechanism built into its structure.

Solving the problem of acid sensitivity

Nothing can be done about the first two factors since the β-lactam ring is vital for antibacterial activity. Without it, the molecule has no useful biological activity at all.

Therefore, only the third factor can be solved. The task then becomes one of reducing the amount of neighboring group participation to make it difficult, if not impossible, for the acyl carbonyl group to attack the β-lactam ring.

Penicillin V has an electronegative oxygen on the acyl side-chain with the electron withdrawing effect required. **The molecule has better acid stability than penicillin G and is stable enough to survive the acid in the stomach.** *Thus, it can be given orally*. However, Penicillin V is still sensitive to **penicillinases** and is slightly less active than penicillin G.

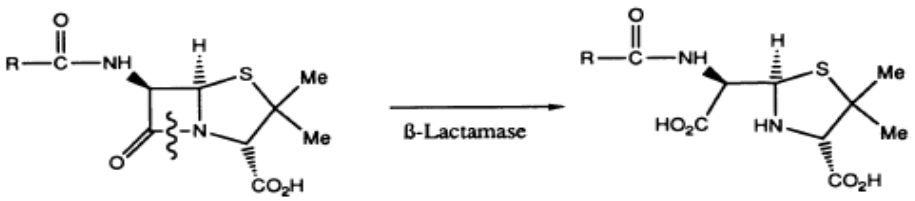
A range of penicillin analogues which have been very successful are penicillins which are disubstituted on the alpha-carbon next to the carbonyl group. As long as one of the groups is electron withdrawing, *these compounds are more resistant to acid hydrolysis and can be given orally* (e.g. **ampicillin** and **oxacillin**).

To conclude, the problem of acid sensitivity is fairly easily solved by having an electron withdrawing group on the acyl side-chain.

B. Penicillin sensitivity to (β-lactamases)

β-Lactamases are enzymes produced by penicillin-resistant bacteria. The same ring opening and deactivation of penicillin which occurred with acid hydrolysis.

The problem of β-lactamases became critical in 1960 when the widespread use of penicillin G led to an alarming increase of *Staph. aureus* infections. These problem strains had gained the lactamase enzyme and had thus gained resistance to the drug.



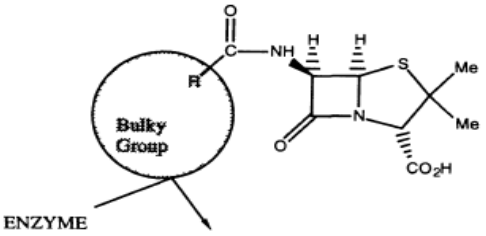
β-Lactamase deactivation of penicillin.

Solving the problem of β-lactamase sensitivity

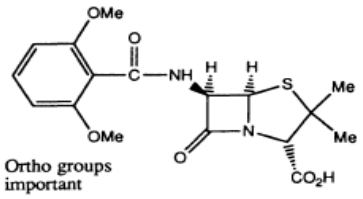
The strategy is to block the penicillin from reaching the penicillinase active site. One way of doing that is to place **a bulky group** on the side-chain. This bulky group can then act as a '**shield**' to ward off the penicillinase and therefore prevent binding.

Methicillin was the first semisynthetic penicillin unaffected by penicillinase and was developed just in time to treat the *Staph. aureus* problem already mentioned.

However, methicillin is by no means an ideal drug. **Since there is no electron withdrawing group on the side-chain, it is acid sensitive**, and so has ***to be injected***.



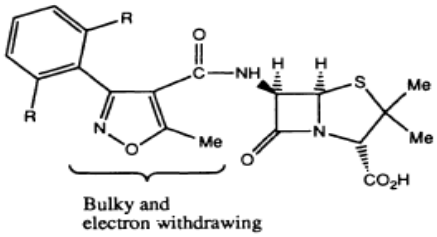
Blocking penicillin from reaching the penicillinase active site.



Methicillin.

These compounds (**oxacillin**, **cloxacillin**, and **flucloxacillin**) are acid-resistant and penicillinase-resistant, and are also useful against *Staph. aureus* infections.

The only difference between the above three compounds is **the type of halogen substitution** on the aromatic ring. Cloxacillin is better absorbed through the gut wall than oxacillin, whereas flucloxacillin is less bound to plasma protein, resulting in higher levels of the free drug in the blood supply.



OXACILLIN R = R' = H
CLOXACILLIN R = Cl, R' = H
FLUCLOXACILLIN R = Cl, R' = F

Incorporation of a five-membered heterocycle.