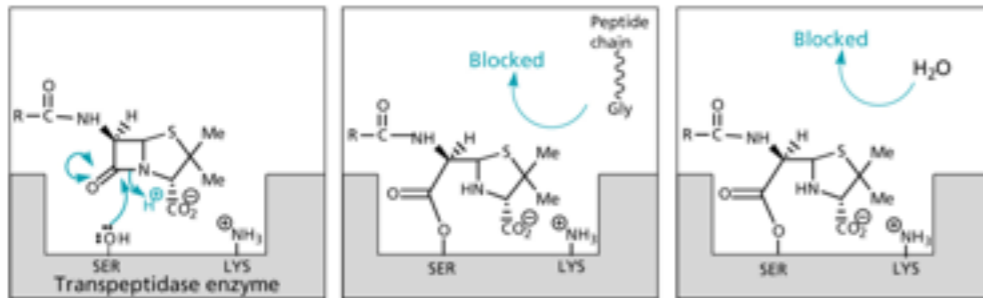


# Schematically...



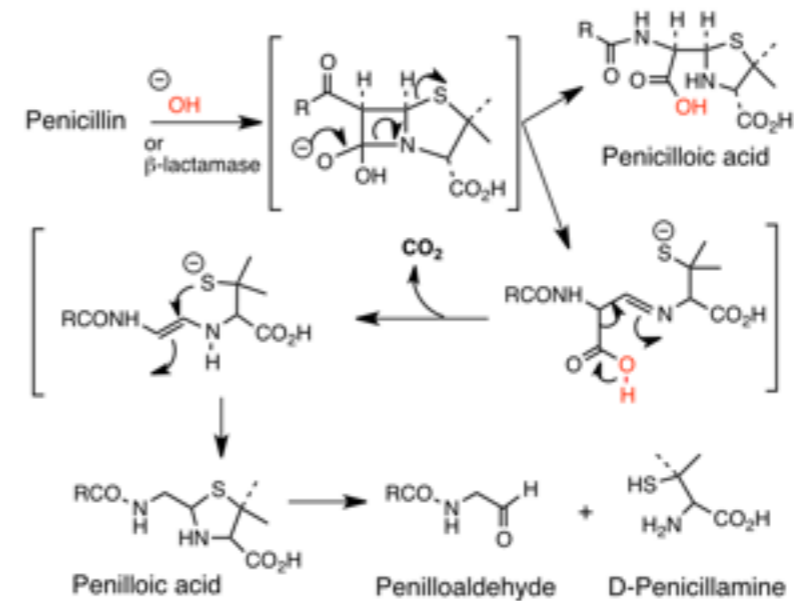
penicillin inhibition

Diagrams and illustrations from Patrick, Intro. to Medicinal Chemistry, 5E  
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"...that which breaks"

## Penicillin Deactivation I

Clinically relevant Instability of  $\beta$ -lactams to Nu: or  $\beta$ -lactamase



Mechanism similar to Penicillin hypersensitivity

"...that which breaks"

## Penicillin Deactivation II

In acidic media



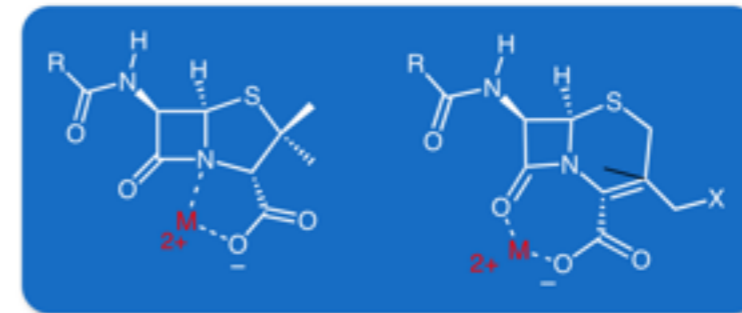
Penicilloic acid fragments further. The main by-product is Penilloic acid

None of these products has antibacterial activity

"...that which bends"

## Penicillin Deactivation III

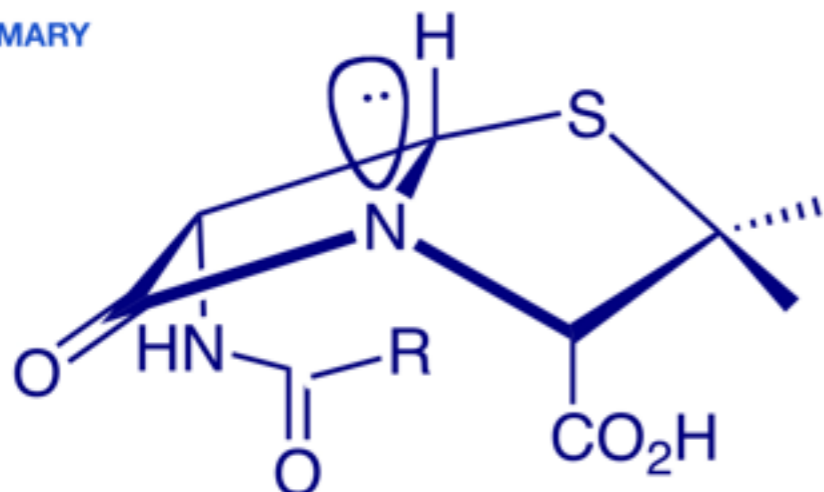
A type of penicillin decomposition is catalysed by heavy metal ions e.g. Hg (also applicable to cephalosporins)



Retarded in buffered solution (pH 6-7)

Water-soluble K & Na salts are used instead

## SUMMARY



Ring-opening: by Nucleophiles,  
Shape-changing: Acid-promoted hydrolysis Chelation

Q1: How does the shape of penicillin influences its chemistry?

Q2: How to improve stability of penicillin derivatives?

## Q2

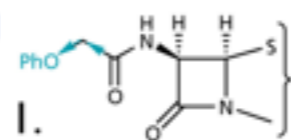
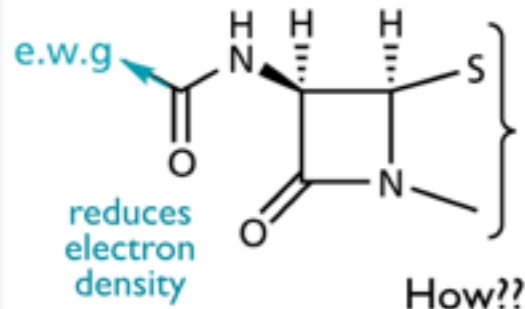
### How to improve the stability of penicillin molecule?

1. Minimise the neighbouring group participation
2. Install Bulky groups

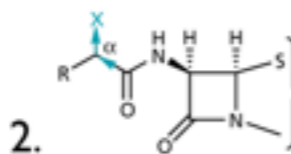
Diagrams and illustrations from Patrick, Intro. to Medicinal Chemistry, 5E

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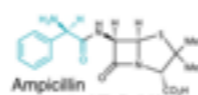
### Minimise the neighbouring group participation



Penicillin V



X = NH<sub>2</sub>, Cl, PhCONH,  
Heterocycles



Ampicillin

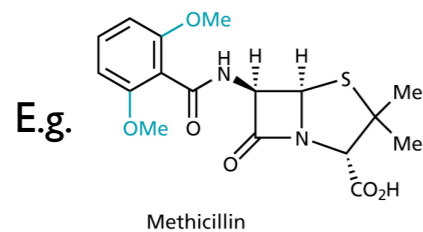
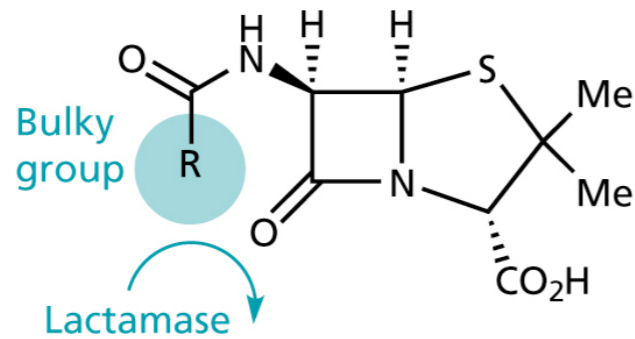
### How to improve the stability of penicillin molecule?

1. Minimise the neighbouring group participation
2. Install Bulky groups

## Penicillinase-resistant penicillin

Blocks the penicillinase enzyme  
but, **Size does matter!**

**The Challenge** to find an appropriate bulky group



- +** steric shield to penicillinase
- No E.W.G
- ⚡ Acid sensitive (Injection)
- 1/50th activity that of Pen G
- Inactive vs. Gram -ve

## Isoxazolyl-substituted penicillins

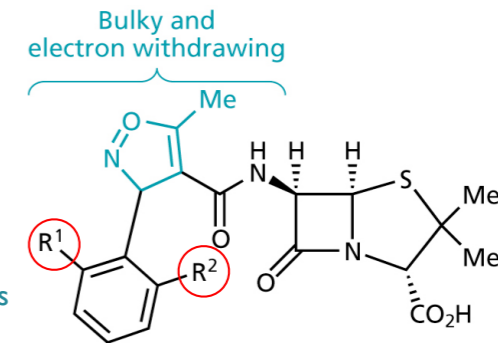
Isoxazolyl ring renders the penicillins:

1. Orally-active
2. Penicillinase-stable

All are useful vs. *S. aureus* infections

Aromatic substitutions of halogens affect the pharmacokinetics & pharmacodynamics of these drugs

But, these afford inferior activity of the original penicillin vs. low penicillinase producing bacteria & Gram -ve



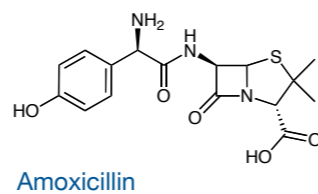
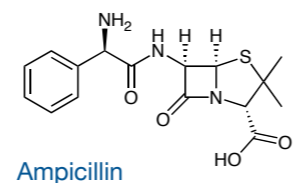
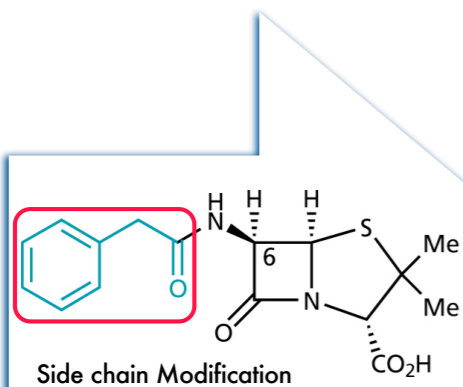
Oxacillin	R <sup>1</sup> = R <sup>2</sup> = H
Cloxacillin	R <sup>1</sup> = Cl, R <sup>2</sup> = H
Flucloxacillin	R <sup>1</sup> = Cl, R <sup>2</sup> = F
Dicloxacillin	R <sup>1</sup> = Cl, R <sup>2</sup> = Cl

Diagrams and illustrations from Patrick, Intro. to Medicinal Chemistry, 5E

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## Broad spectrum Penicillins

Narrow



## Broad spectrum penicillins

similar to Pen G, but with improved activity vs. Gram -ve cocci & enterobacteria

hydrophilic C<sub>α</sub> to the carbonyl grp → acid-resistant, oral

no steric shield: penicillinase-sensitive

non-toxic

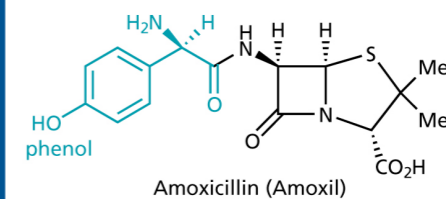
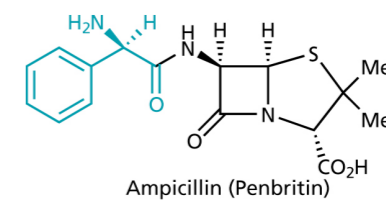
amoxicillin is usually co-administered with clavulanic acid → broaden its spectrum of activity

absorption thro' the gut wall is a problem for these antibiotics

the free amino and carboxylic acid groups are dipolar → prodrugs

the phenol grp in amoxicillin → gives better absorption

## Ampicillin & Amoxicillin



## SUMMARY

Penicillin G: Shape, Amide Chemistry

Penicillin V: Chemistry (EWG)

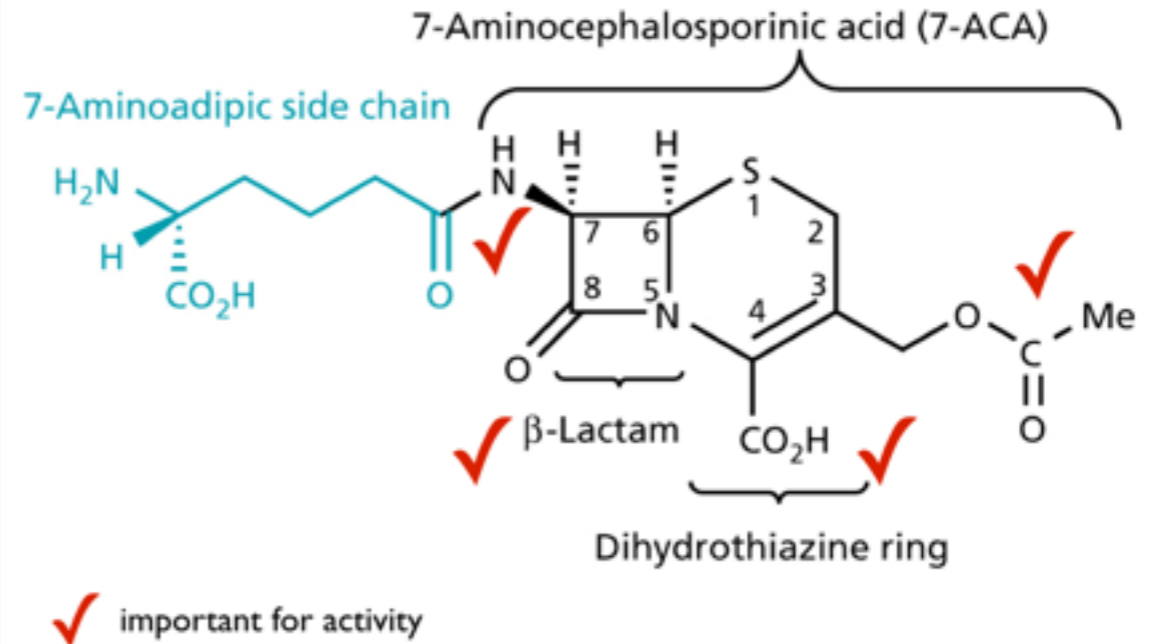
Methicillin: Chemistry (Bulky group), Injection

Isoxazolyl-substituted Pen: Chemistry (2-in-1)



Ampicillin, Amoxicillin  
 Chemistry (EWG, NH<sub>2</sub>), Oral, Prodrug

## Cephalosporin C

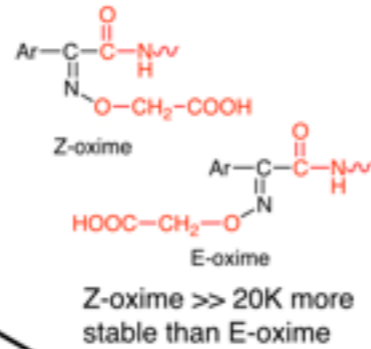


## Substituents, SAR of Cephalosporins

### α, α' position

L-isomer of >> 30 times than D-isomer

Addition of methoxyoxime improves stability by 100-fold



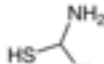
Ar=



furan



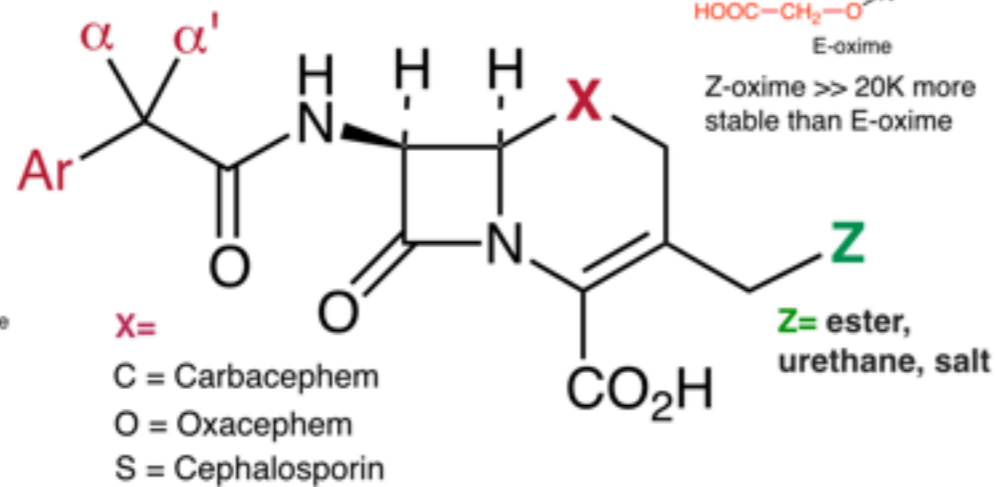
thiophene



aminothiazole



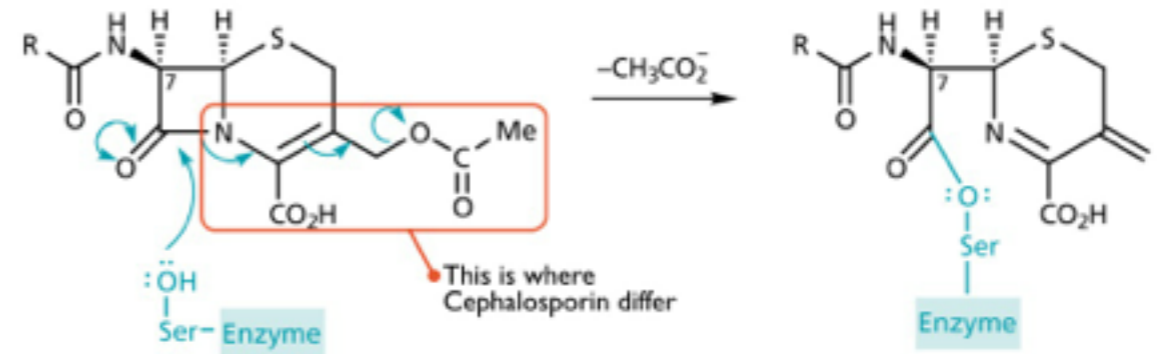
phenyl



## How do cephalosporins work?

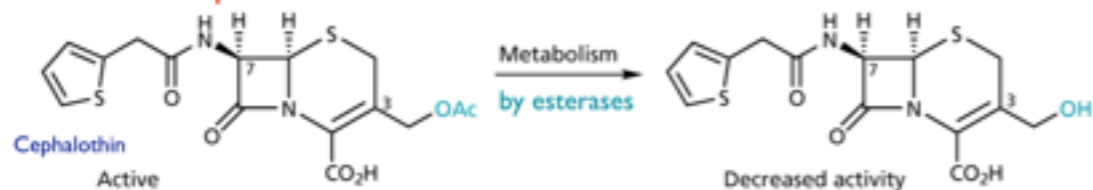
Similar to Pens

Except for the involvement of acetoxy group at 3-position

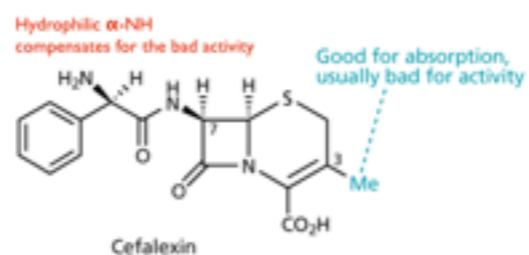
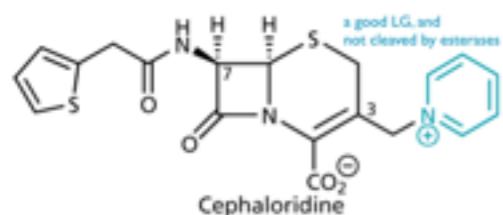


## Cephalosporins

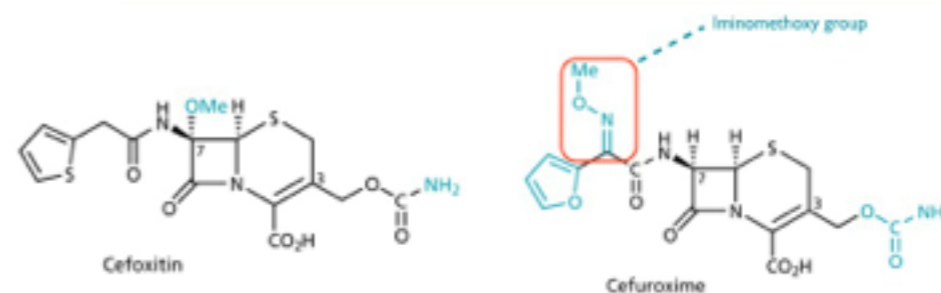
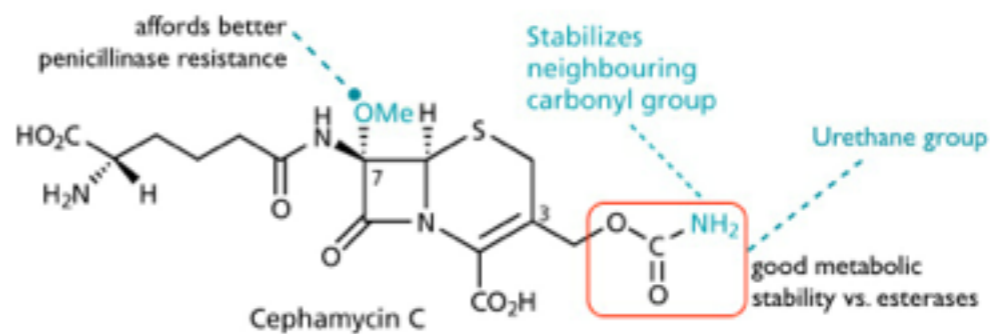
### 1st Gen: The problem



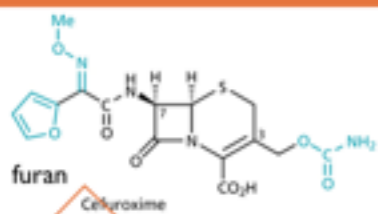
### Solutions



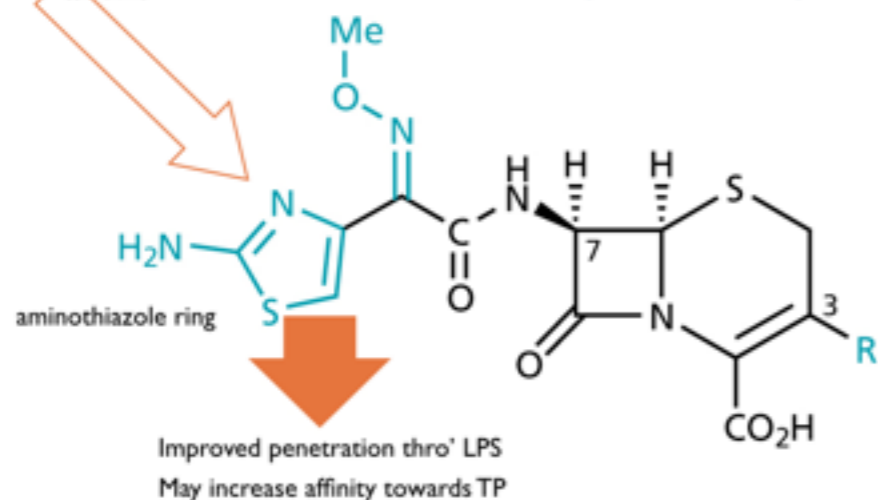
## Second Gen Cephalosporins - Cephameycins



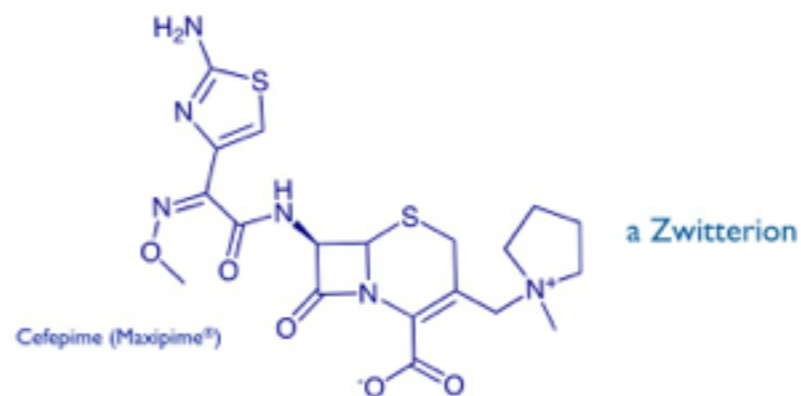
## Third Gen Cephalosporins



- Problems of Gen 2 agents  
 Can't get in (Permeability) & Get pushed out (Porins)
- Developed to fight the growing multi-resistance of Gram -ve bacteria e.g. *Pseudomonas aeruginosa* & *Enterobacter*



## Fourth Gen Cephalosporins - Oximinoceph.

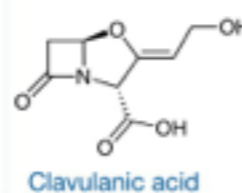
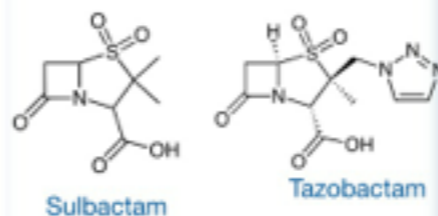


- much higher stability against many common plasmid- and chromosomally-mediated  $\beta$ -lactamases;
- tremendous improvement in its penetration via LPS
- good affinity towards transpeptidases
- expanded spectrum of activity vs. Gram +ve and -ve

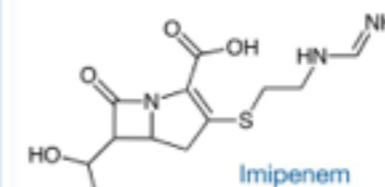
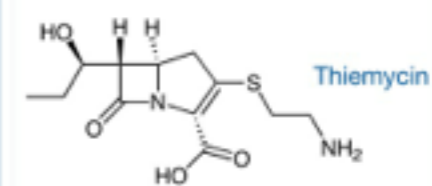
Other beta lactams...

## β-lactamase inhibitors

### Class I



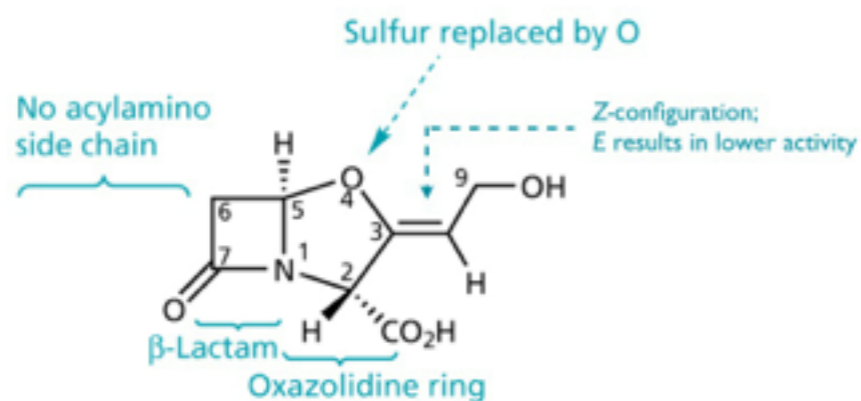
### Class II



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## β-lactamase inhibitors - Clavulanic acid



**Poor antibiotic activity!**

Irreversible inhibitor of beta lactamases

Co-administered with :  
Amoxicillin (Augmentin) & Ticarcillin (Timentin)

## β-lactamase inhibitors: Carbapenam core

