

# تفريغ هيديسنال 2



المحاضرة: Penicillin Part 2  
Rehat Zyoud  
الصيدلاني/ة:



لجان الرفعات

# Bacterial Resistance:

- Two types:
- 1. Natural (innate) resistance, this is particularly important in gram negative (G-) bacteria mediated by the reduced permeability of the outer cell envelope of Gram negative bacilli which is linked to the cell wall via the peptidoglycan, such cell envelope is not present in gram positive bacteria
- 2. Other normally resistant bacteria can develop resistance by generating resistance enzymes by mutation or natural selection

# Bacterial Resistance:

- The second type of enzymatic resistance is the most common resistance mechanism.
- The resistant enzymes are collectively known as “penicillinases” and are of two general types:
  - 1. B-lactamases (most important) → *إنزيم الذي تفرزه البكتيريا*
  - 2. Acylases

حكيانا انه هذا ال enzyme الي بيكسر ال  
Penicillin ( يعطى رح يبطل فعال

ال gram+ تطلق ال Penicillase  
Extracellular عنشان صيد ال Penicillin  
رح يلتف بهذا ال enzyme ما يوصل  
البكتيريا رح يكسر

ال gram- تطلق ال Penicillase  
Periplasmic يعطى داخل ال Cell-membran

# $\beta$ -lactamase (Penicillinase):

$\beta$ -lactamase break the  $\beta$ -lactam ring, they are either  
chromosomal or plasmid, constitutive or inducible  
depending on particular species:

تتحفز لما تتعرض ال Penicillin  
اصلا " موجودة داخل البكتيريا بضمن النظر عن البيوت  
حسب نوعي البكتيريا  
لهم تصنيفهم

- Gram +ve *S.aureus*: 1. **inducible**  $\beta$ -lactamase  
2. synthesized at cell wall and **released extracellularly**

95% of *S.aureus* became resistant to penicillins

- Gram -ve bacillic 1. **constitutive R-factor**  
2. Cytoplasmic enzymes
- هو ال بيكسر ال  
Penicilline

Again  $\beta$ -lactamase from different species are different in structure and properties.

# $\beta$ -lactamase (Penicillinase):

- Gram +ve bacteria normally release  $\beta$ -lactamase to outside of the cell that will cleave penicillin before reaching the bacteria.
- Gram -ve bacteria release  $\beta$ -lactamase into the periplasmic space, which again will cleave penicillin before reaching the plasma membrane.
- Penicillin has to reach the plasma membrane where the transpeptidase present to do its antibacterial action.
- Most of gram -ve bacteria are  $\beta$ -lactamase producing bacteria

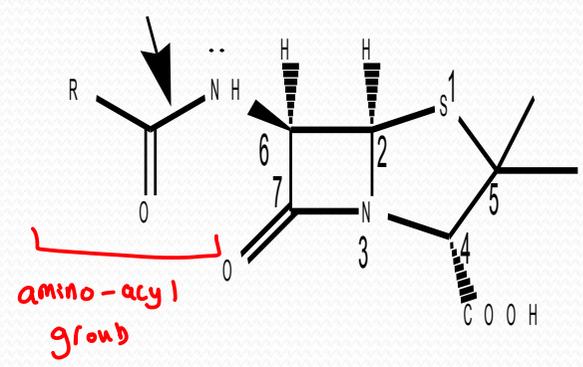
كيف هل الـ Penicillase في بي بي

بيكسروا الـ penicillin في الحيوان بلا في الـ Acylase

ح يكسروا الـ acyl amino group

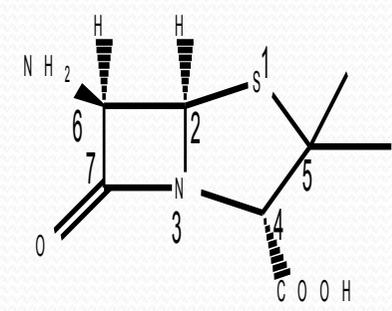
# 2. Acylases

- These enzymes can hydrolyze the acylamino-side chain of penicillins



حكيانها  
activity

Acylase



6-Amino penicillanic Acid (6-APA)

# Rules to create Penicillinase resistant Penicillins

كيف اخلق ال Penicillin تقاوم ال Penicillanase  
بيدي ايان صا يدخل ال Binding site ال Penicillanase  
ال بخلق ال  $\alpha$  جزى من aromatic ring و خلونا نروح للملايه الجامع

- Increase the steric bulk at the  $\alpha$ -carbon on the acyl-amino group enhances good penicillins activity
- Antibacterial activity is enhanced when the  $\alpha$ -carbon is part of aromatic ring, so based on these points we can conclude that Ortho substituted aromatic ring should produce excellent  $\beta$ -lactamase resistance
- See the following slide for examples.

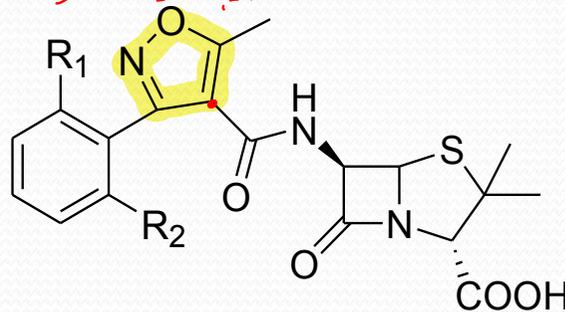


# Isoxazoyl Penicillins

حظية isoxazol ring

اول ايجي خليتها اربعة جزء منها

② فيها N, O واد 2 يعتبرها طيب شو صار ملك  
good withdrawing group



$R_1, R_2 = H$

Oxacillin

$R_1 = Cl, R_2 = H$

Cloxacillin

$R_1 = Cl, R_2 = F$

Flucloxacillin

$R_1, R_2 = Cl$

Dicloxacillin

## Flucloxacillin: (how to think and analyze)

- Bulky which means  $\beta$ -lactamase resistant
- E-withdrawing which means acid stable
- $\alpha$ -carbon is part of an aromatic ring which means good activity

① resistant to  $\beta$ -lactamase

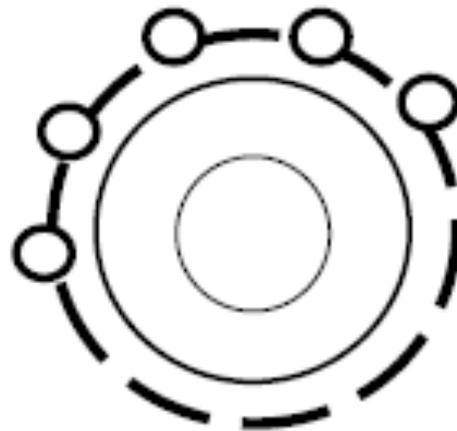
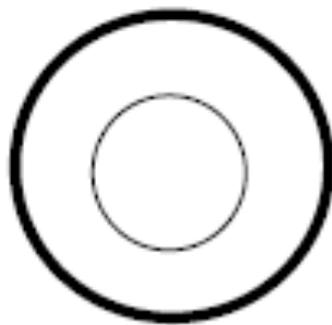
② oral active

بس مع هيك ال Penicillin G

افوى منه والدكتور اذا بلاف انه الريفيت بحاجة لـ  $\beta$ -lactamase resistance يعطيه صابى المجموعه

- Bulkier substituents are required for small sized heterocycles to give good anti- $\beta$ -lactamase activity
- Acid stable due to the electron withdrawing effect of the isoxazole ring.
- Used against *S.aureus* resistant bacteria.
- Most penicillinase-resistant penicillins are less active than Penicillin G or Phenoxymethyl penicillin (V) against most non- $\beta$ -lactamase procedures that are normally sensitive to penicillins, increasing  $\alpha$  carbon bulkiness is with price
- Penicillinase-resistant penicillins tend to be bulky and lipophilic with poor penetration into Gram negative bacteria cell envelope

G+ve  
-Thick cell wall  
-Cell Membrane



G-ve  
-Thinner cell wall  
-Inner Cell Membrane  
-Outer membrane with porins

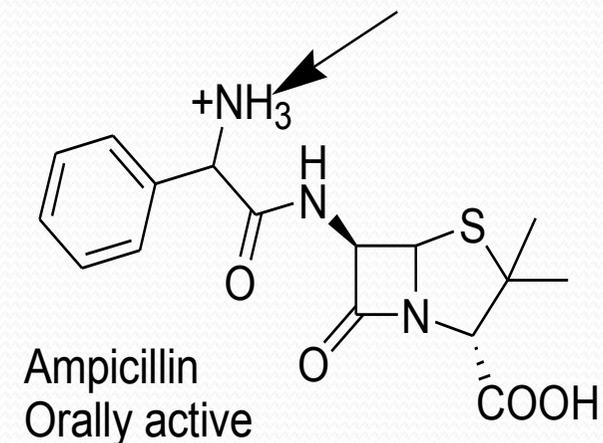
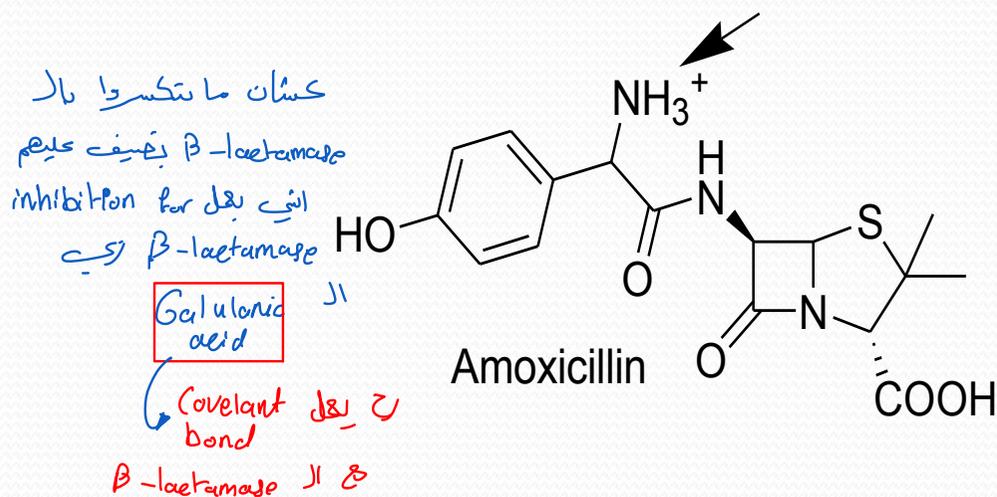


# Broad Spectrum Penicillins

- Very important finding is the fact that substitution of  $\alpha$ -carbon with polar or ionized group will produce wide spectrum of activity including Gram negative bacteria It works against (Pseudomonas, E.coli, Haemophilus influenza, ...)

Amino Penicillin  
broad spectrum  
افضل انبي ال  
درعتبر

In plasma PH NH2 will become ionized to NH3+



# Broad Spectrum Penicillins

Ampicillin and Amoxicillin are effective against Gram negative genera E.Coli, Klebsiella, Haemophila, Salmonella, Shiegella and some proteus

Ampicillin and Amoxicillin largely retain Gram positive activity

D-isomer is more active than the L-isomer

The extended activity of  $\alpha$ -amino-benzyl-penicillin is not due to the anti- $\beta$ -lactamase resistant activity rather it is due to the hydrophilic nature of the molecule which enables it to penetrate the outer cell-envelope through the porin channels

# Broad Spectrum Penicillins

- $\alpha$ -OH also expand the activity but they are less active than the  $\alpha$ -NH<sub>2</sub> derivatives and less acid-stable than the  $\alpha$ -amino group

- $\alpha$ -COOH has wide spectrum activity including all the bacteria that are  $\alpha$ -NH<sub>2</sub> sensitive as well as gram negative bacilli of the genera “**Pseudomonas**, Klebsiella, Enterobacter and Proteus” however its potency against Ampicillin-Sensitive bacteria is lower than Ampicillin

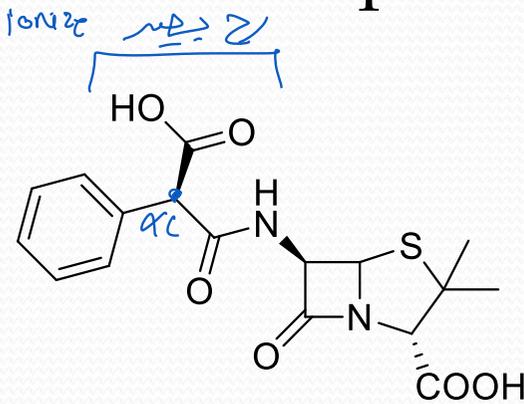
اذا اشتمت  
على الفعالية  
تسمى  
لدرجة انها  
تكون  
Pseudomonas



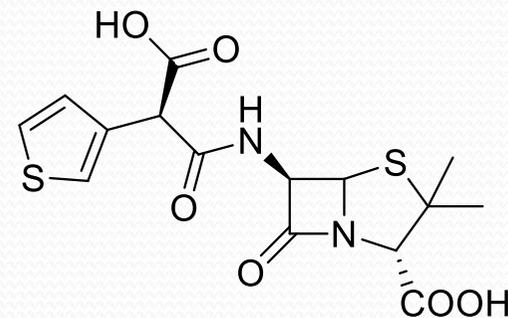
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# Carboxypenicillins

- They have a carboxylic acid at the  $\alpha$ -carbon of the acyl side chain.
- They have broad spectrum activity.



Carbenicillin



Ticarcillin

Not given orally  $\rightarrow$  لأنه يحيد بالتكسر بالمعدة

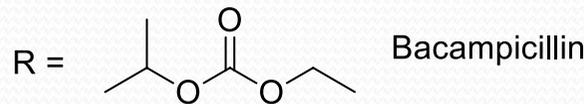
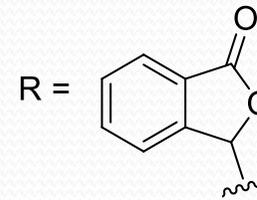
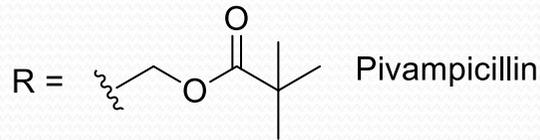
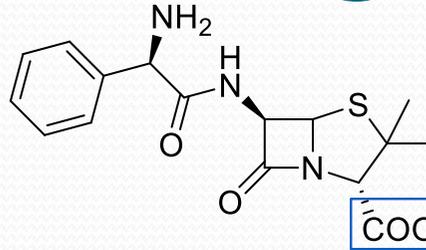
الامتصاص قليل

# Ampicillin and amoxicillin prodrugs

- Ampicillin and amoxicillin are Poorly absorbed through the mucus membrane, this is due to the fact that they formed a zwitter ionic molecule at physiological pH (they contain a carboxylic acid and an amino group in their structure).

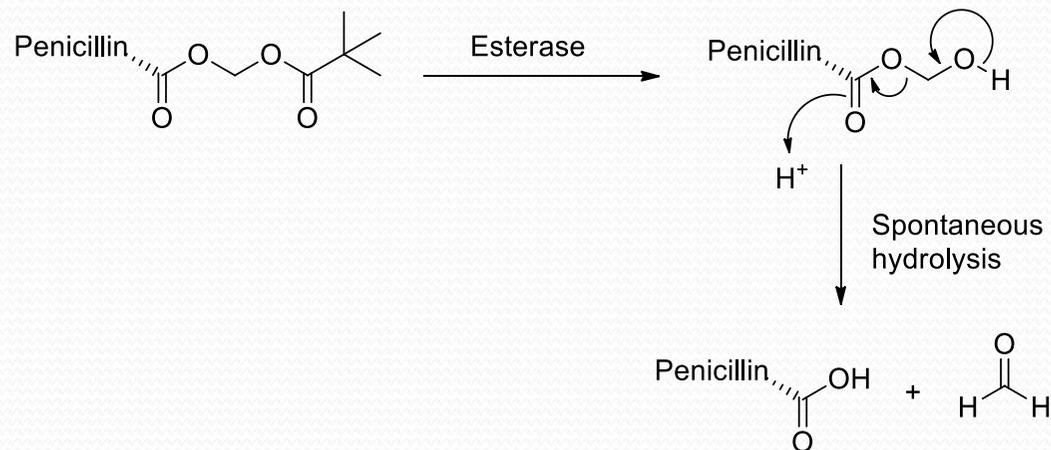
لا يمتصوا  
للسلائد الجايه
- The oral bioavailability can be improved by masking one of them, mainly the carboxylic acid.... By preparing a prodrug esters.

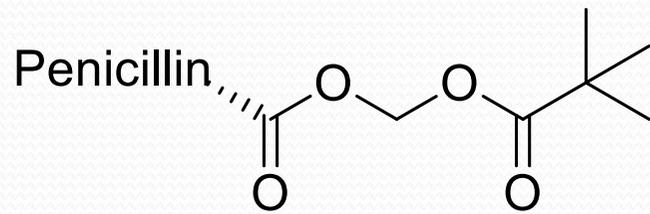
# Ampicillin prodrugs



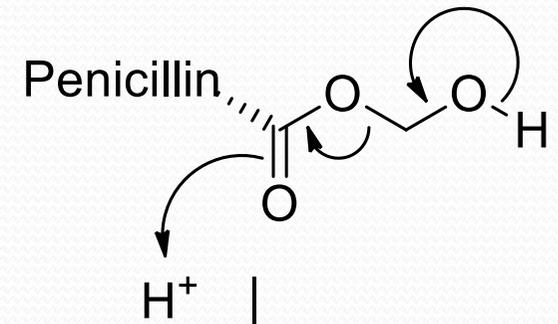
الـ (COOH) افضل مكان  
لـ عمل Pro-drug عملنا  
ester و به تكسر  
بالـ esterase و يترجع  
لـ active form  
هناك حسنة  
الـ absorption

- The methyl ester did not give the same improvement in absorption and activity (why?).

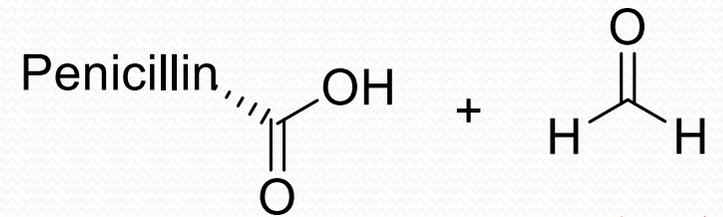




ester link

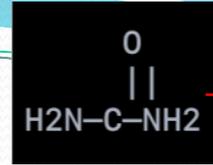


Spontaneous hydrolysis



Penicillin + Formaldehyd

Urea group تقريبا ال Urea  
 Pseudomonas ال spectrum كثر كبير روح توصل ال



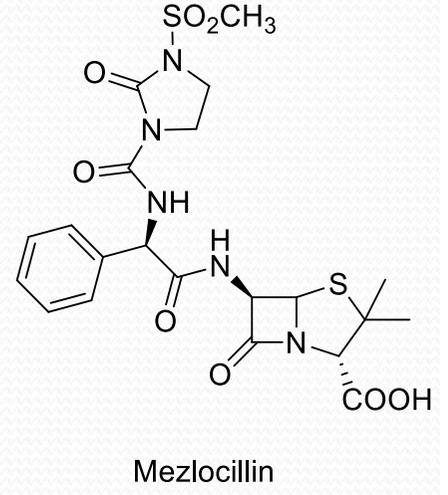
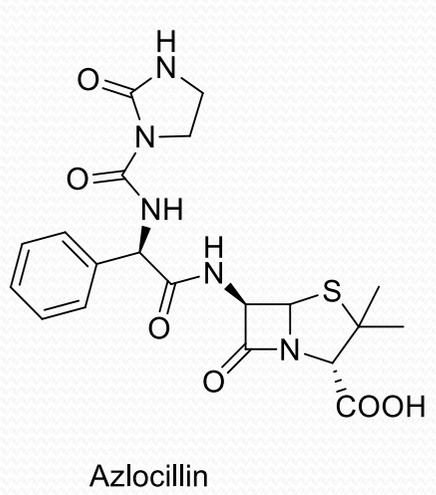
هاي ال Urea



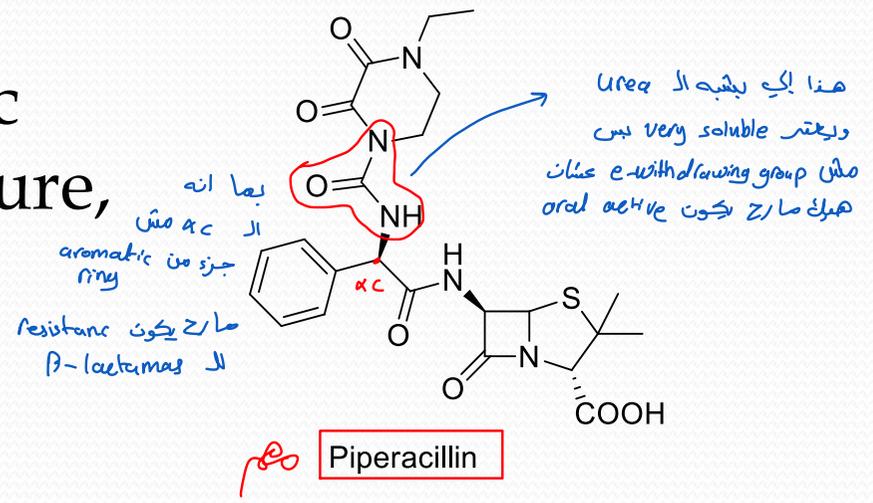
# Ureidopenicillins

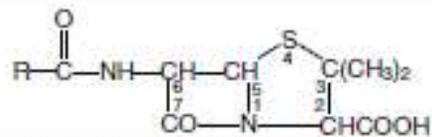
- They all have a urea group at the  $\alpha$ -carbon in the acyl side chain.
- They have better activity compared to amoxicillin and they are more resistant to  $\beta$ -lactamase.

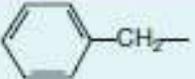
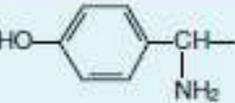
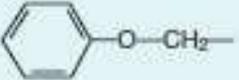
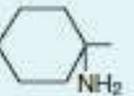
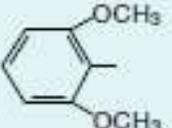
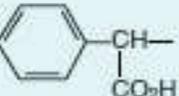
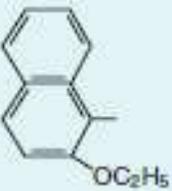
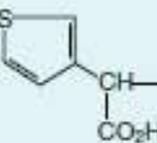
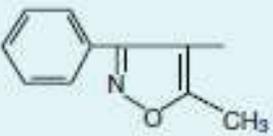
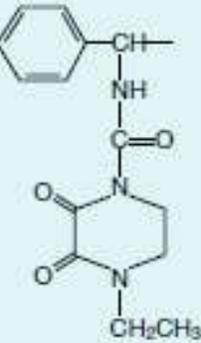
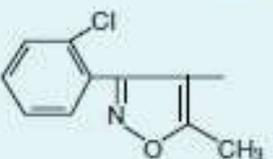
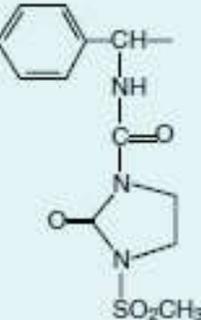
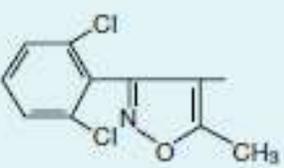
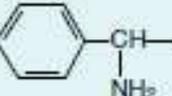
ال جزء



- Used parenterally for gram -ve infections especially *P.aeruginosa*.
- the ureido group though to mimic some of the peptidoglycan structure, which means that it can bind to penicillin-binding protein





Generic Name	Chemical Name	R Group	Generic Name	Chemical Name	R Group
Penicillin G	Benzylpenicillin		Amoxicillin	<i>o</i> - $\alpha$ -Amino- <i>p</i> -hydroxybenzylpenicillin	
Penicillin V	Phenoxymethylpenicillin		Cyclacillin	1-Aminocyclohexylpenicillin	
Methicillin	2,6-Dimethoxyphenylpenicillin		Carbenicillin	$\alpha$ -Carboxybenzylpenicillin	
Nafcillin	2-Ethoxy-1-naphthylpenicillin		Ticarcillin	$\alpha$ -Carboxy-3-thienylpenicillin	
Oxacillin	5-Methyl-3-phenyl-4-isoxazolylpenicillin		Piperacillin	$\alpha$ -(4-Ethyl-2,3-dioxo-1-piperazinylcarbonylamino)benzylpenicillin	
Cloxacillin	5-Methyl-3-(2-chlorophenyl)-4-isoxazolylpenicillin		Mezlocillin	$\alpha$ -(1-Methanesulfonyl-2-oxoimidazolidinocarbonylamino)benzylpenicillin	
Dicloxacillin	5-Methyl-3-(2,6-dichlorophenyl)-4-isoxazolylpenicillin				
Ampicillin	<i>o</i> - $\alpha$ -Aminobenzylpenicillin				

**TABLE 8.3** Classification and Properties of Penicillins

Penicillin	Source	Acid Resistance	Oral Absorption (%)	Plasma Protein Binding (%)	$\beta$ -Lactamase Resistance ( <i>S. aureus</i> )	Spectrum of Activity	Clinical Use
Benzylpenicillin	Biosynthetic	Poor	Poor (20)	50–60	No	Intermediate	Multipurpose
Penicillin V	Biosynthetic	Good	Good (60)	55–80	No	Intermediate	Multipurpose
Methicillin	Semisynthetic	Poor	None	30–40	Yes	Narrow	Limited use
Nafcillin	Semisynthetic	Fair	Variable	90	Yes	Narrow	Limited use
Oxacillin	Semisynthetic	Good	Fair (30)	85–94	Yes	Narrow	Limited use
Cloxacillin	Semisynthetic	Good	Good (50)	88–96	Yes	Narrow	Limited use
Dicloxacillin	Semisynthetic	Good	Good (50)	95–98	Yes	Narrow	Limited use
Ampicillin	Semisynthetic	Good	Fair (40)	20–25	No	Broad	Multipurpose
Amoxicillin	Semisynthetic	Good	Good (75)	20–25	No	Broad	Multipurpose
Carbenicillin	Semisynthetic	Poor	None	50–60	No	Extended	Limited use
Ticarcillin	Semisynthetic	Poor	None	45	No	Extended	Limited use
Mezlocillin	Semisynthetic	Poor	Nil	50	No	Extended	Limited use
Piperacillin	Semisynthetic	Poor	Nil	50	No	Extended	Limited use