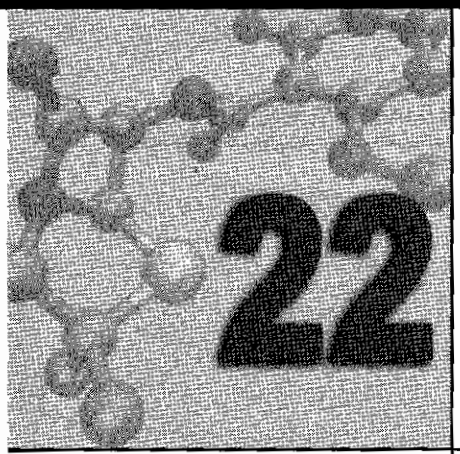


22 ANTIBIOTICS

INTRODUCTION

Antibiotics are substances produced by various species of microorganisms (bacteria, fungi, actinomycetes) that suppress the growth of other microorganisms and eventually may destroy them. Since their discovery in the 1930s, antibiotics have made it possible to cure diseases caused by bacteria such as pneumonia, tuberculosis and meningitis—saving the lives of millions of people around the world.

Historically, the most common classification has been based on chemical structure and proposed mechanism of action as follows:

1. Agents that inhibit the synthesis of bacterial cell walls; these include the penicillins and cephalosporins, which are structurally similar and dissimilar agents, such as cycloserine, vancomycin, bacitracin and the imidazole antifungal agents.
2. Agents that act directly on the cell membrane of the microorganisms affecting permeability and leading to leakage of intracellular compounds; these include polymyxin, polyene antifungal agents, nystatin and amphotericin B that bind to cell wall sterols.
3. Agents that affect the function of 30S and 50S ribosomal subunits to cause reversible inhibition of protein synthesis; these include tetracyclines, erythromycins, chloramphenicol and clindamycin.
4. Agents that bind to the 30S ribosomal subunit and alter protein synthesis, which eventually leads to cell death; these include aminoglycosides.
5. Agents that affect nucleic acid metabolism such as rifamycins, which inhibit DNA-dependent RNA polymerase.

β-LACTAM ANTIBIOTICS

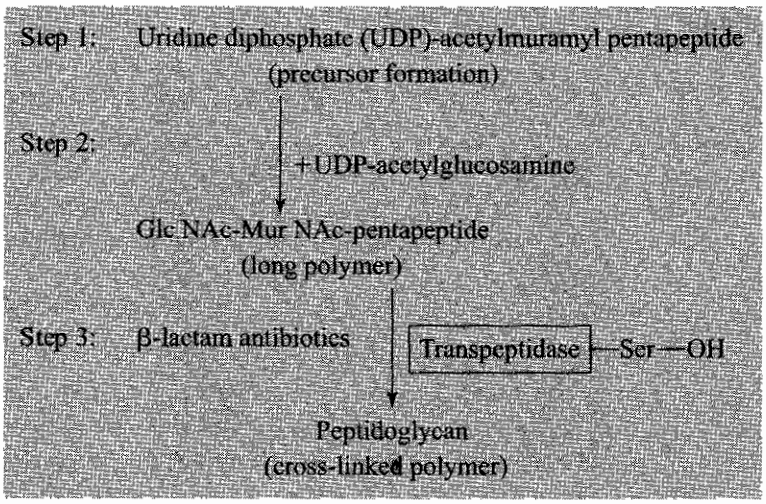
Antibiotics that contain the β-lactam (a four-membered cyclic amide) ring structure constitute the dominant class of agents currently employed for the chemotherapy of bacterial infections. Penicillin, cephalosporin and their semi-synthetic derivatives come under this class.

Mechanism of action

The cell wall of bacteria is essential for the normal growth and development. Peptidoglycan is a heteropolymeric component of the cell wall that provides rigid mechanical stability by virtue of its highly cross-linked latticewise structure.

The peptidoglycan is composed of glycan chains, which are linear strands of two alternating amino sugars (*N*-acetyl glucosamine and *N*-acetyl muramic acid) that are cross-linked by peptide chains.

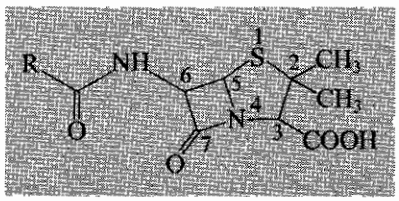
The biosynthesis of peptidoglycan involves three stages:



The last step in peptidoglycan synthesis is inhibited by β-lactam antibiotics. The transpeptidase enzyme that contains serine is probably acylated by β-lactam antibiotics with cleavage of —CO—N—bond of the β-lactam ring. This renders the enzyme inoperative and inhibits peptidoglycan synthesis.

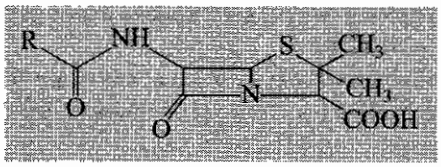
PENICILLINS

The penicillins are commonly named as penams, a designation in which the sulphur atom is given the top priority.

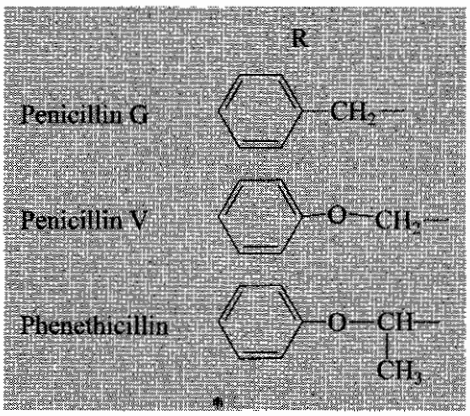


Using this nomenclature, the penicillins have a prerequisite carboxylic acid group placed at the C-3 position. The west-end substituents are joined to the C-6 centre and are usually substituted via acylation, thus constituting a variety of C-6 acylamido substituents. The β-lactam carbonyl centre is located at position 7 and the C-2 centre contains a geminal dimethyl substitution characteristic of penicillins.

Classification



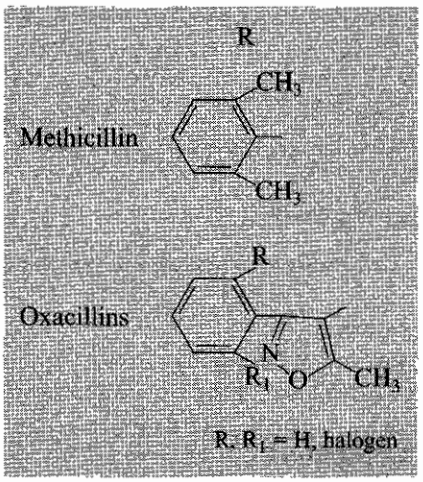
Early penicillins



General impact on antibacterial activity:

1. Excellant gram-positive potency against susceptible *Staphylococci, Streptococci.*
2. Useful against some gram-positive cocci.
3. Good oral absorption but relatively acid-labile.
4. Ineffective against gram-negative bacilli.
5. Susceptible by deactivation by penicillinase.

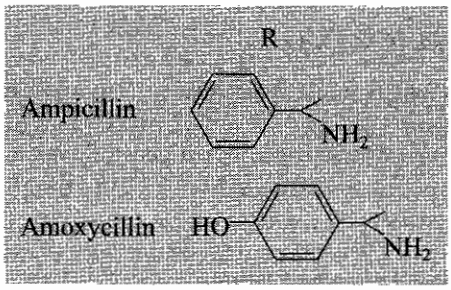
Penicillinase-resistant penicillins



General impact on antibacterial activity:

1. Diminished susceptibility to many penicillinases; active against microorganisms resistant to early penicillins.
2. Oxacillins offer good oral activity.
3. Inadequate spectrum against many gram-negative species.

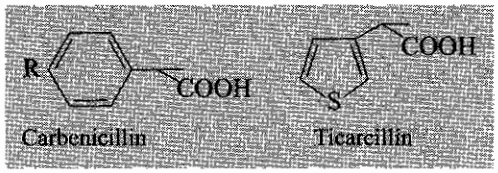
Broad-spectrum penicillins



General impact on antibacterial activity:

1. Extended spectrum of activity against some gram-negative bacteria; retention of gram-positive potency.
2. Generally well absorbed orally; ampicillin can be dosed IV., I.M. as well; amoxycillin exceptional oral agent.
3. Prodrug esters (of ampicillin) enhance systemic drug levels.
4. Ineffective against *Pseudomonas aeruginosa*.

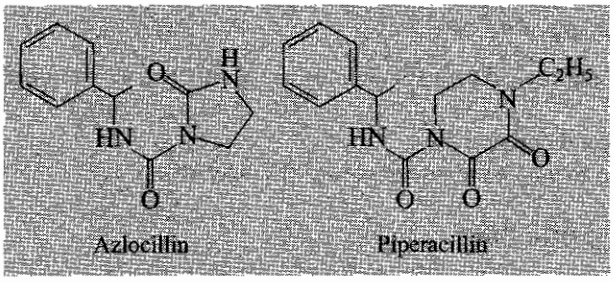
Anti-pseudomonal penicillins



General impact on antibacterial activity:

1. Extended spectrum of activity against many pathogenic gram-negative bacteria; reduced gram-positive potency.
2. Good activity against *P. aeruginosa*.
3. Oral absorption, chemical stability problematic.
4. Prodrug esters (of carbenicillin) enhance systemic drug levels.

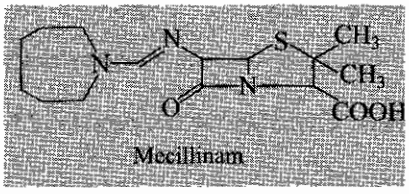
Broad-spectrum ureido penicillins



General impact on antibacterial activity:

1. Enhanced spectrum of activity against *P. aeruginosa*, expanded activity against *Klebsiella, Serratia, Proteus*.
2. Good potency against gram-positive bacteria; but generally not effective against penicillinase producers.
3. Good pharmacokinetic profile.

Penicillin with a C-6 amidino west-end

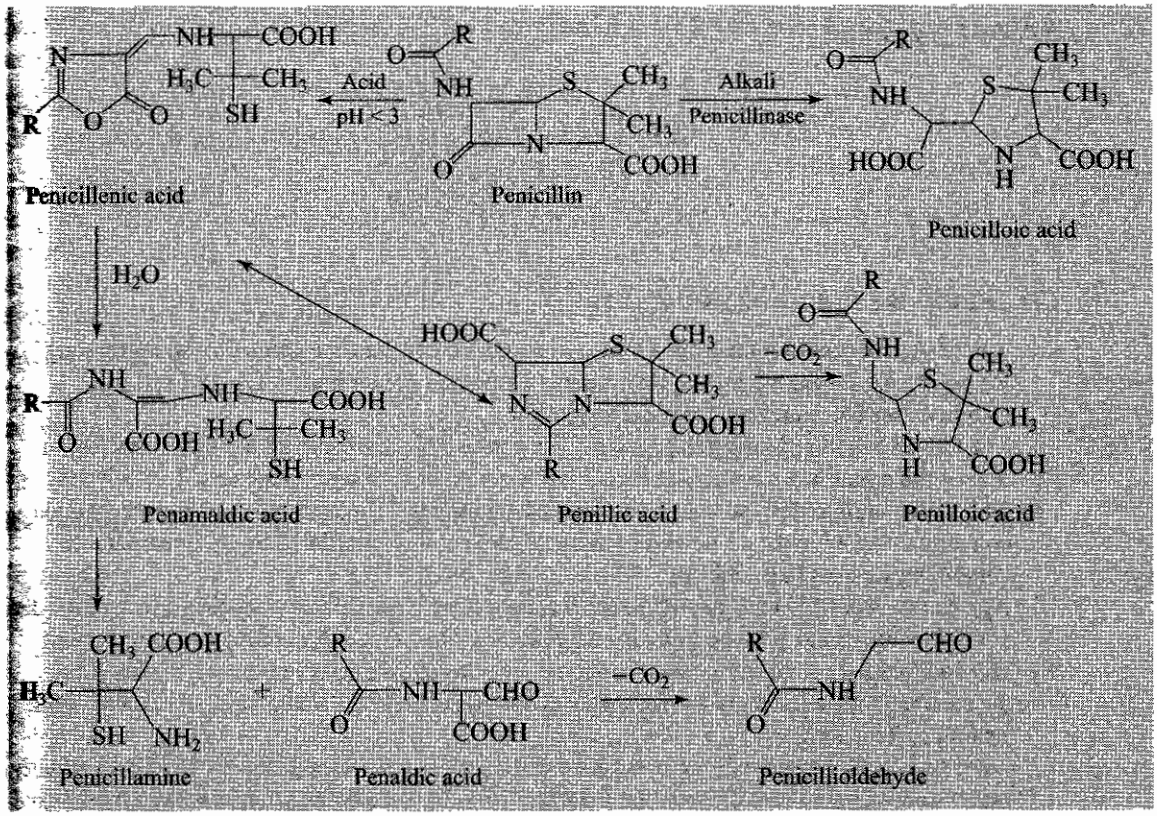


1. Good activity against *E. coli, Klebsiella, Shigella, Salmonella* and many other resistant species.
2. Inactive against *P. aeruginosa*.
3. Prodrug esters enhance systemic drug levels.

Mechanism

Refer β-lactam antibiotics.

Chemical degradation of penicillins



In strongly acidic solutions (pH < 3), penicillin undergoes a complex series of reactions leading to a variety of inactive degradation products. Similarly, penicillinase enzyme hydrolyses the β-lactam ring to produce inactive penicilloic acid.

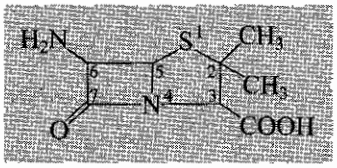
Acid-catalysed degradation in stomach contributes in a major way to the poor oral absorption of penicillin. Thus, efforts to obtain penicillins with improved pharmacokinetic and microbiologic properties have sought to find acyl functionalities that would minimise sensitivity of the β-lactam ring to acid hydrolysis and, at the same time, maintain antibacterial activity.

Substitution of an electron-withdrawing group in the α-position of benzyl penicillin has stabilised the penicillin to acid-catalysed hydrolysis. The increased stability imparted by such electron-withdrawing groups has been attributed to a decrease in reactivity of the side-chain amide carbonyl oxygen atom towards participation in β-lactam ring-opening to form the penicillenic acid.

Adverse effects

Penicillins cause hypersensitivity reactions (allergy) in several percent of patients, which may be due to the formation of an antigenic penicilloyl proteins formed *in vivo* by the reaction of nucleophilic groups (e.g. ϵ-amino) on specifie body proteins with the β-lactam carbonyl groups.

SAR of penicillin



C-6 amino west end substitution

a. The design and development of the west-end substituents has been aimed at strengthening various weaknesses which have traditionally hampered penicillins in terms of activity, stability, resistance and absorption/distribution.
b. The C-6 amine moiety itself is necessary for appreciable antibacterial activity, but substitution of the amine via monoacylation can offer much more potent congeners.
c. Only carboxamido derived west-end moieties are tolerated; sulphonation or phosphoramide containing substituents are devoid of antibacterial activity. Similarly, imide or carbamate containing west-end are inferior.
d. Agents that were stable to penicillinase enzymes were created by introducing a more crowded environment around β-lactam moiety. Methicillin contains 2,6-dimethoxy benzamido west-end and the placement of methoxy groups on the aromatic ring is important; the bis *ortho* arrangement creates the most effective crowding around thc β-lactam carbonyl centre, while retaining good activity.

   The oxacillins contain a 5-methyl-3-phenyl-4-isoxazolyl west-end substituents that similarly impose crowding in proximity to the β-lactam ring. In these compounds, both the methyl and phenyl substituents are positioned closest to β-lactam system. Removal of either group increases susceptibility to penicillinases.
e. To expand the antibacterial spectrum of penicillins, more hydrophilic west-end were designed and that can cnhance potency against gram-negative pathogens. Ampicillin contains a D-α-aminophenylacetamido west-end and is most recognised as amino penicillins. In general, substituents on the phenyl ring are detrimental either due to decreased hydrophilicity or conversely, due to adverse polar effects if an ionizable substituent is present. A notable balance of these opposing forces has been achieved with the placement of a *para*-hydroxyl group onto the phenyl ring. Amoxycillin is essentially comparable to ampicillin in terms of *in vitro* potency, but displaces better oral efficacy.
f. The spectrum of activity was further expanded with introducing strong acidic groups at the α-carbonyl centre of the side-chain. Thcse imparted useful potency against *P. aeruginosa*. Carbenicillin possesses α-carboxyphenylacetamido west-end.
g. The acylation of the ampicillin west-end amine functionality with certain polar groups leads to cyclic urea derivatives; ureido penicillins (azlocillin) which contain a five-membered cyclic urea system joined via, *N*-acylation to the α-amino substituent of ampicillin. These

are more active against *P. aeruginosa* than carbenicillin and have potency against other gram-negative pathogenic species. The presence of urea group imparts improved penetration into these gram-negative species traditionally resistant to penicillins.

Substituents at sulphur

Sulphur is the only atom at position 1 of the penicillin in order to retain appreciable antibacterial activity.

C-2 substituents

The geminal dimethyl group at C-2 is characteristic of the penicillin.

C-3 substituents

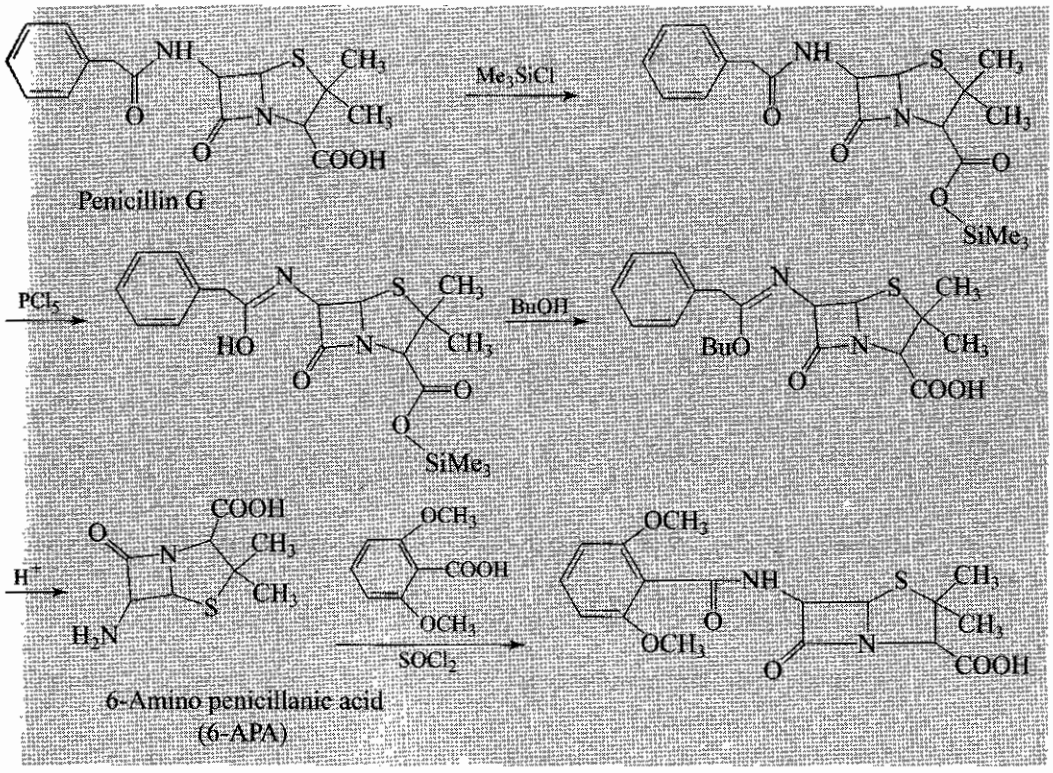
In general, derivatisation of the C-3 carboxylic acid functionality is not tolerated unless the free penicillin carboxylic acid can be generated *in vivo*. Doubly activated penicillin esters, such as alkanoyloxyalkyl congeners undergo rapid cleavage *in vivo* to generate active penicillin, e.g. pivampicillin and becampicillin.

Variation at N-4

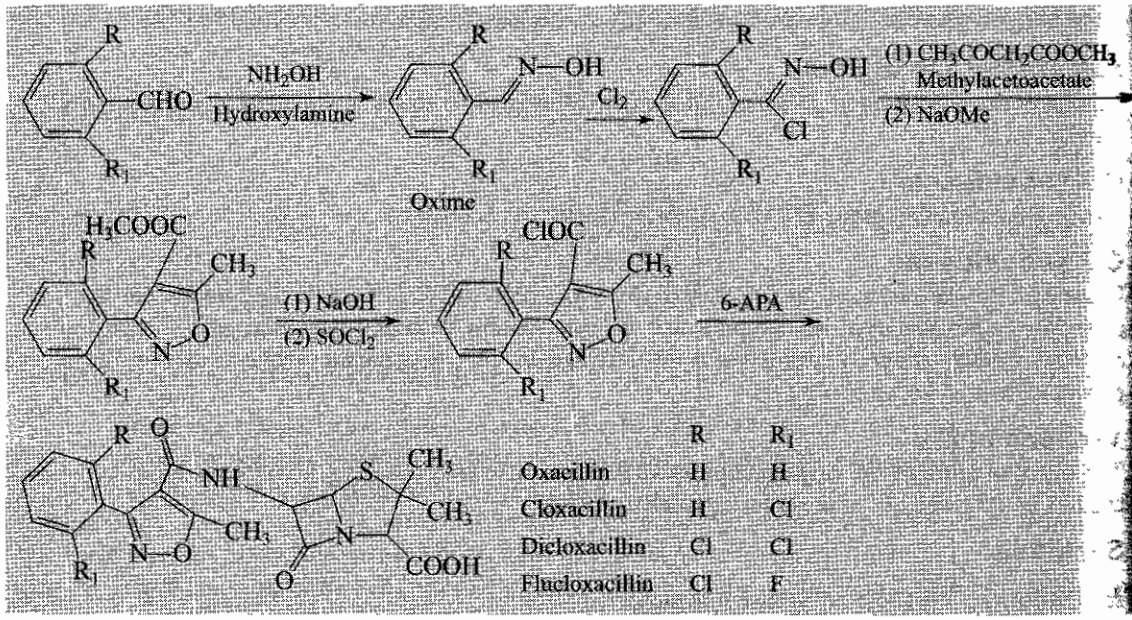
The nitrogen atom at the ring junction is vital for antibacterial activity; the nitrogen atom contributes to the reactivity of the β-lactam carbonyl centre.

Synthesis

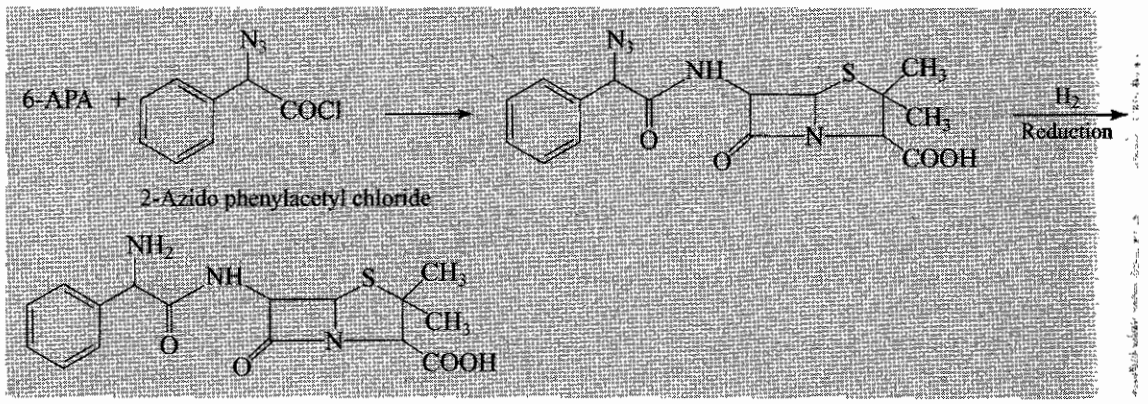
Methicillin 2,6-Dimethoxy phenyl penicillin.



Oxacillins Isoxazolyl penicillins.

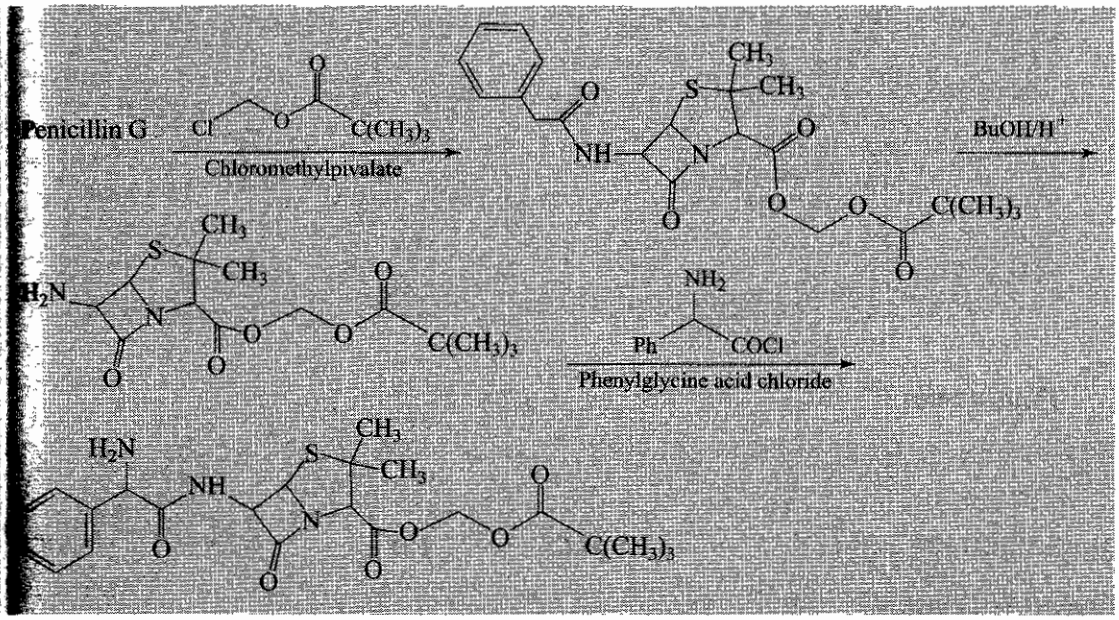


Ampicillin 6-[D-α-aminophenylacetamido] penicillinic acid.



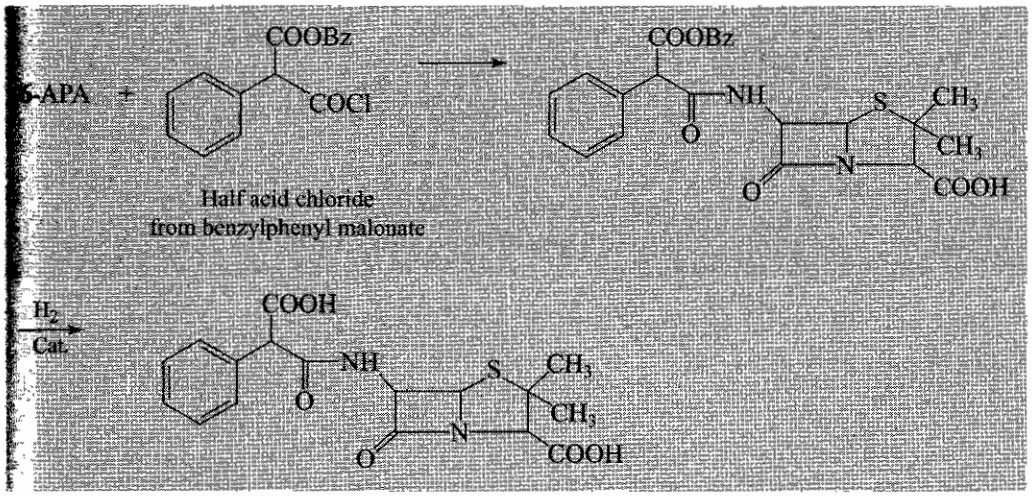
The corresponding product from acylation with 2-azido-4-hydroxyphenylacetylchloride is amoxycillin.

Pivampicillin



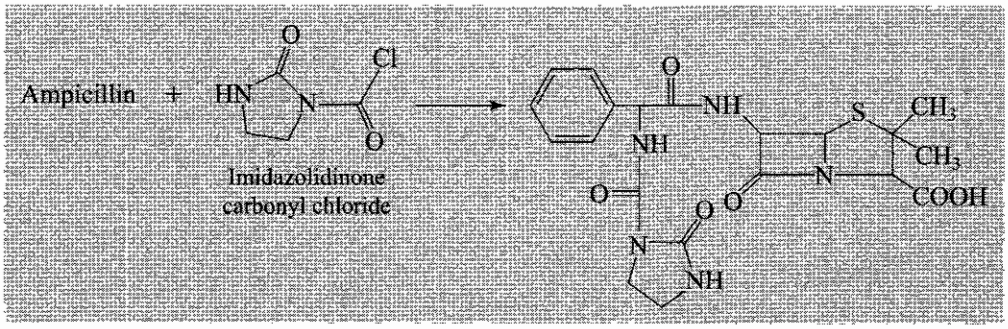
It is a prodrug for ampicillin. *In vivo*, the esters are hydrolysed back to the parent ampicillin.

Carbenicillin α-carboxy benzyl penicillin.

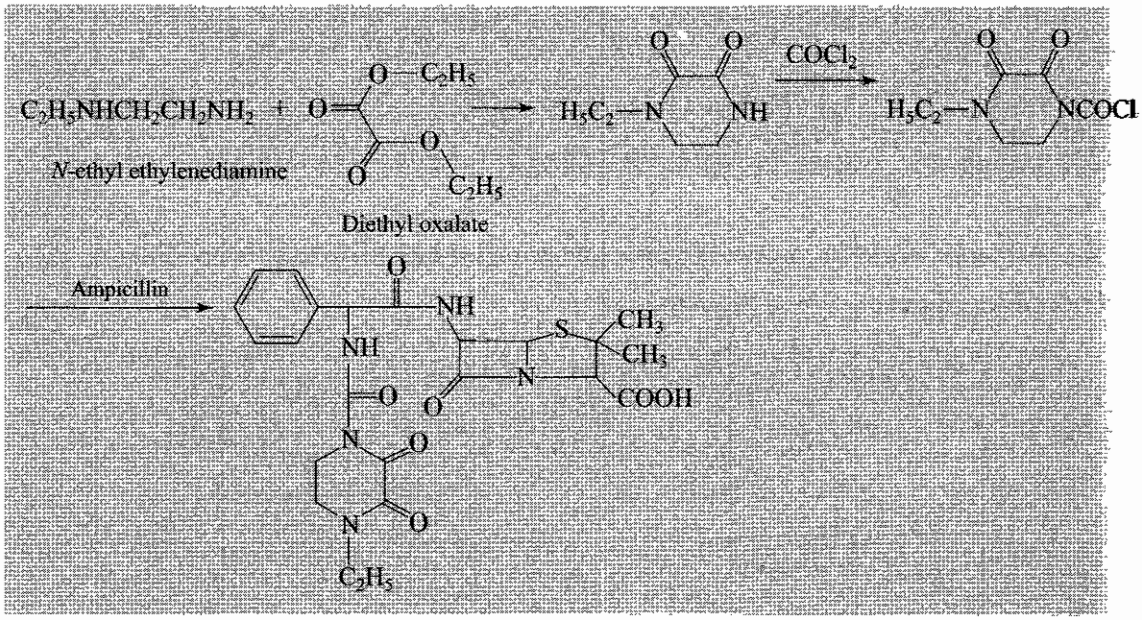


A similar sequence starting with 3-thiophenyl malonic acid leads to the ticarcillin.

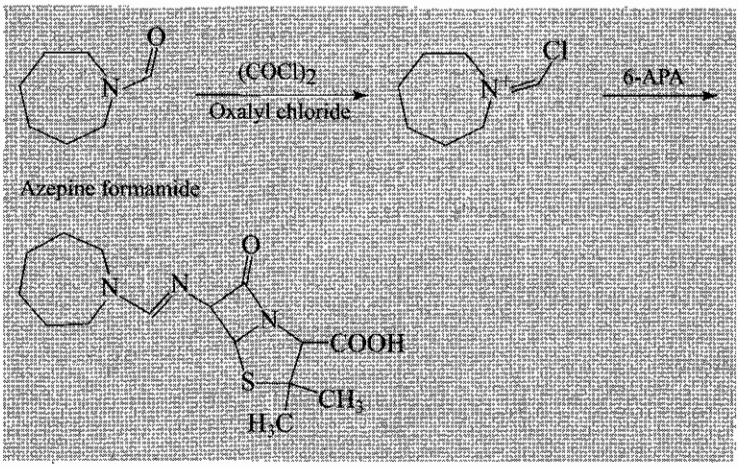
Azlocillin



Piperacillin



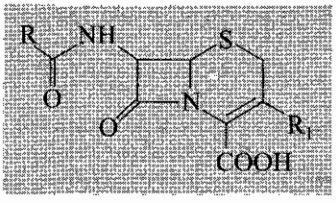
Mecillinam (amidinocillin)



CEPHALOSPORINS

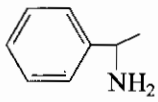
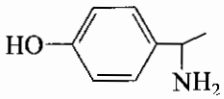
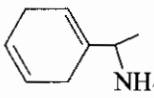
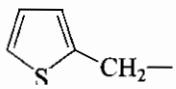
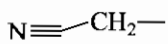
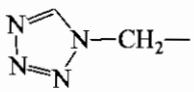
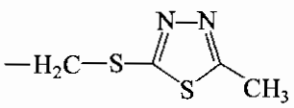
The cephalosporins are β-lactam antibiotics isolated from cephalosporium species and/or prepared semi-synthetically. This comes under the class of 7-amino cephalosporonic acid (7-ACA) derivatives and are much more acid-stable than the corresponding 6-APA compounds. The cephalosporins have a mechanism of action similar to that of penicillins, mainly, they inhibit the cross-linking of the peptidoglycan units in bacterial cell wall by inhibiting transpeptidase enzyme.

Classification



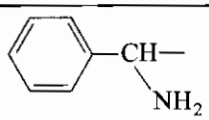
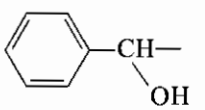
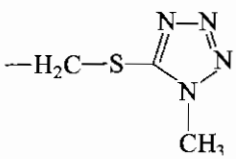
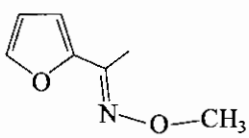
First-generation cephalosporins

These drugs have the highest activity against gram-positive and the lowest activity against gram-negative bacteria.

	R	R_1
Cephalexin		CH_3
Cefadroxil		CH_3
Cephradine		CH_3
Cephalothin		$—CH_2OCOCH_3$
Cephacetrile		$—CH_2OCOCH_3$
Cefazolin		

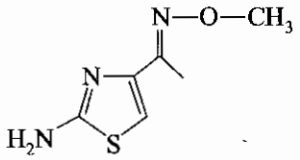
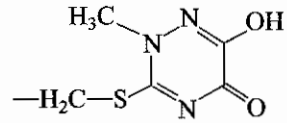
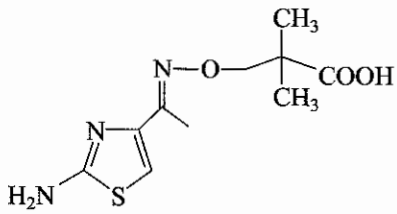
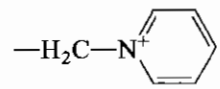
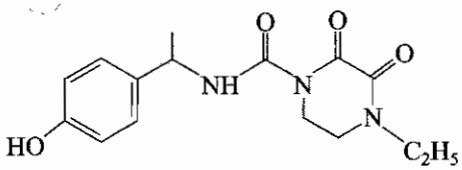
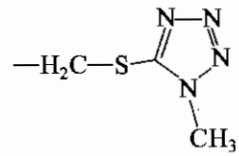
Second-generation cephalosporins

These drugs are more active against gram-negative and less active against gram-positive bacteria than first-generation members.

	R	R_1
Cefaclor		Cl
Cefamandole		
Cefuroxime		$—CH_2OCONH_2$

Third-generation cephalosporins

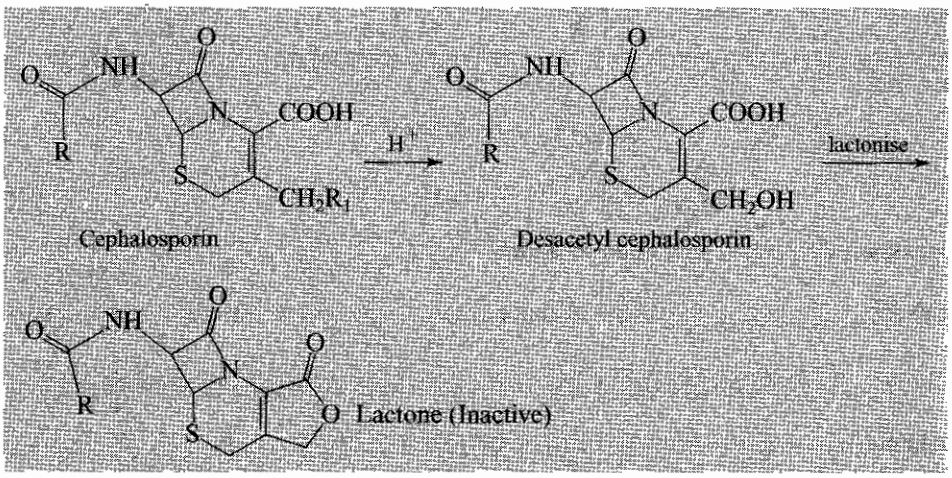
These drugs are less active than first-generation drugs against gram-positive but have a much expanded spectrum of activity against gram-negative organisms.

	R	R_1
Cefotaxime		$-CH_2OCONH_2$
Ceftizoxime	Same as above	H
Ceftriaxone	Same as above	
Ceftizidime		
Cefoperazone		

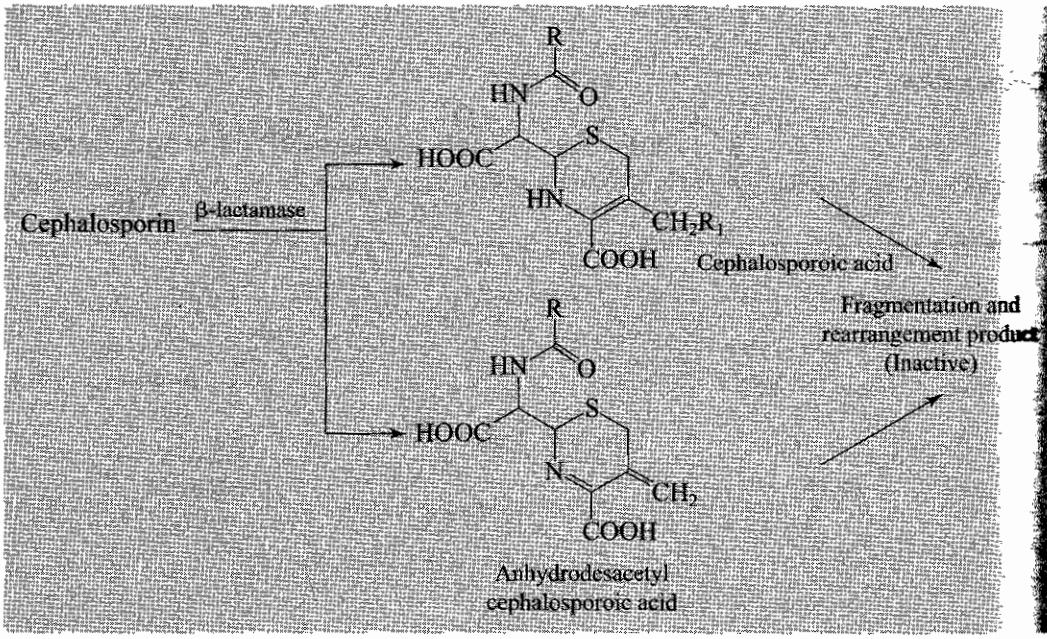
Degradation of cephalosporins

Cephalosporins experience a variety of hydrolytic degradation reactions.

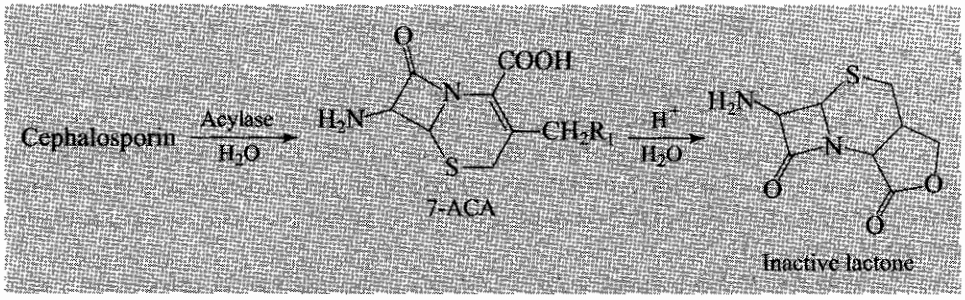
In strong acid solution



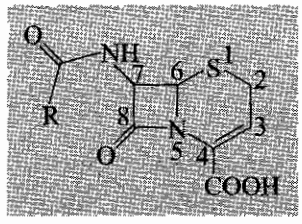
In the presence of β-lactamase



In the presence of acylase



SAR of cephalosporins



1. 7-Acylamino substituents

   a. Acylation of amino group generally increases the potency against gram-positive bacteria, but it is accompanied by a decrease in gram-negative potency.
   b. High antibacterial activity is observed only when the new acyl groups are derived from carboxylic acids for gram-positive bacteria.
   c. Substituents on the aromatic ring phenyl that increases lipophilicity provide higher gram-positive activity and generally lower gram-negative activity.
   d. The phenyl ring in the side-chain can be replaced with other heterocycles with improved spectrum of activity and pharmacokinetic properties, these include thiophene, tetrazole, furan, pyridine and aminothiazoles.

2. C-3 substituents

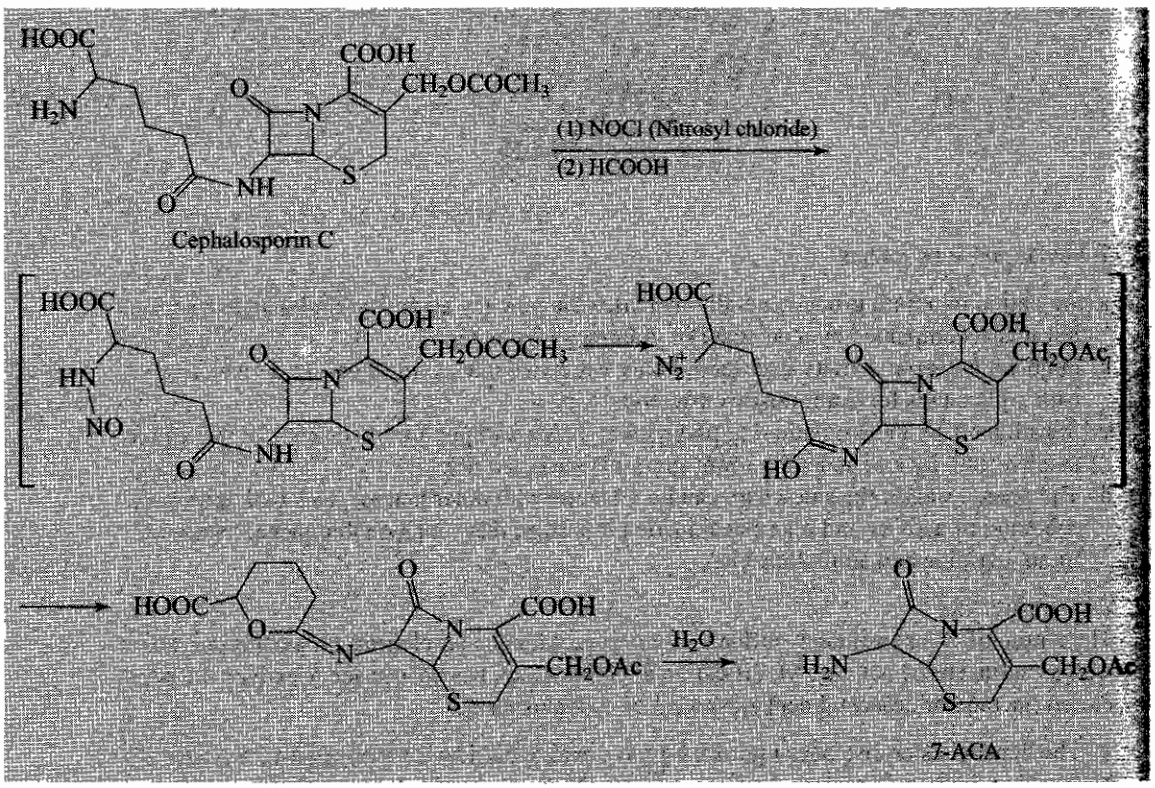
   The nature of C-3 substituents influences pharmacokinetic and pharmacological properties as well as antibacterial activity. Modification at C-3 position has been made to reduce the degradation (lactone of desacetyl cephalosporin) of cephalosporins.

   a. The benzoyl ester displaces improved gram-positive but lower gram-negative activity.
   b. Pyridine, imidazole replaced acetoxy groups show improved activity against *P. aeruginosa*. Displacement of acetoxy group by azide ion yields derivatives with relatively low gram-negative activity.
   c. Displacement with aromatic thiols of 3-acetoxy group results in an enhancement of activity against gram-negative bacteria with improved pharmacokinetic properties.
   d. Replacement of acetoxy group at C-3 position with—CH_3, Cl has resulted in orally active compounds.

3. Cephamycins
   Introduction of C-7 a-methoxy group shows higher resistance to hydrolysis by β-lactamases.
4. Oxidation of ring sulphur to sulphoxide or sulphone greatly diminishes or destroys the antibacterial activity.
5. Replacement of sulphur with oxygen leads to oxacepam (latamoxef) with increased antibacterial activity, because of its enhanced acylating power. Similarly, replacement of sulphur with methylene group (loracarbef) has greater chemical stability and a longer half-life.
6. The carboxyl group of position-4 has been converted into ester prodrugs to increase bioavailability of cephalosporins and these can be given orally as well, e.g. cefuroxime axetil, cefodoxime proxetil.
7. Olefinic linkage at C-3-4 is essential for antibacterial activity. Isomerisation of the double-bond to 2-3 position leads to great losses in antibacterial activity.

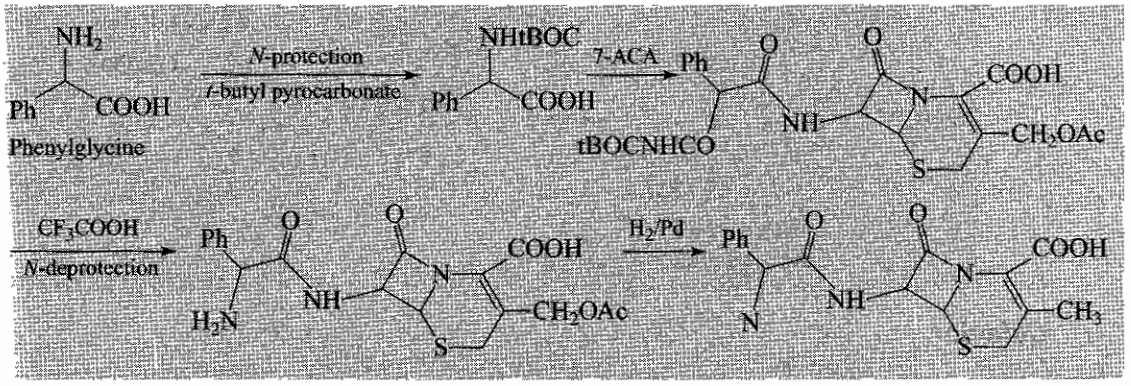
Synthesis

7-Aminocephalosporonic acid from cephalosporin C

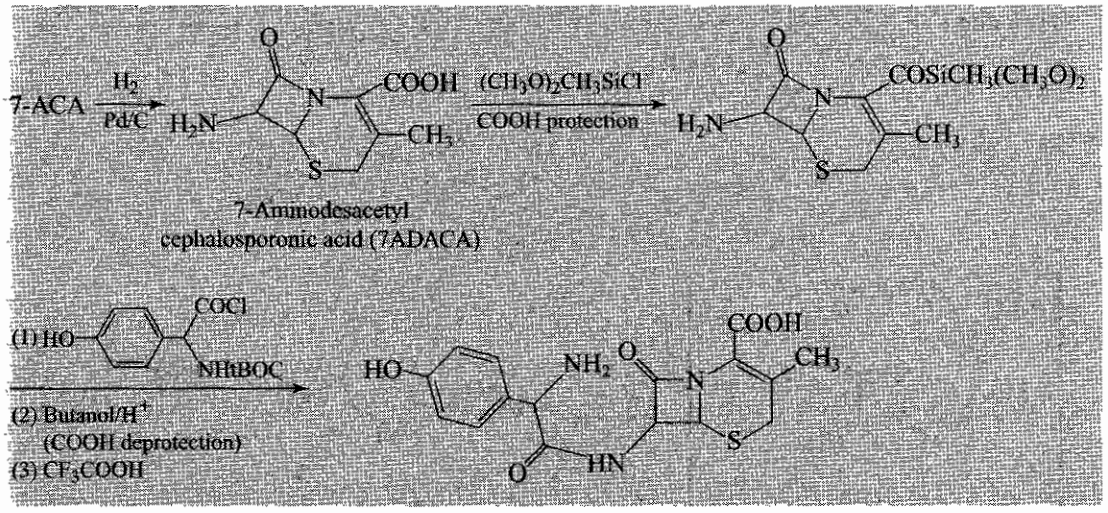


Cephalosporin C is isolated on an industrial scale by fermentation using *Cephalosporium acremonium*.

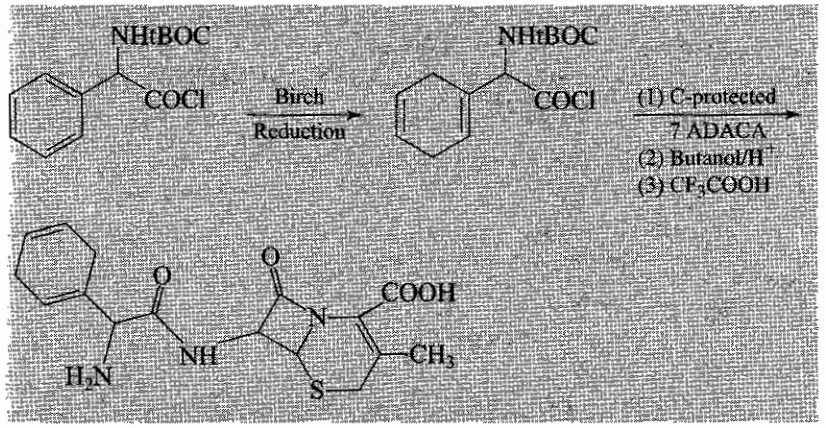
Cephalexin



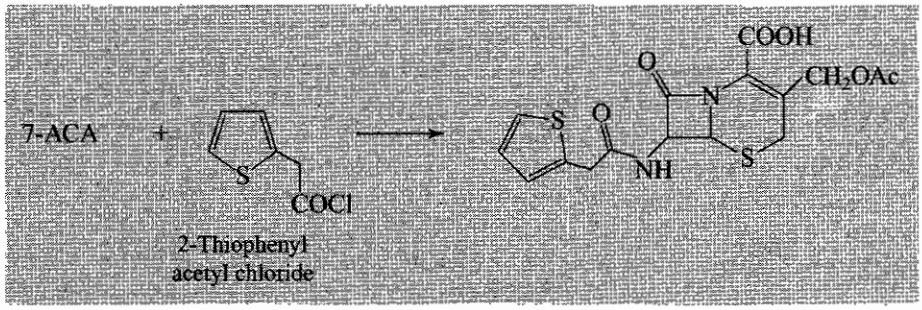
Cefadroxil



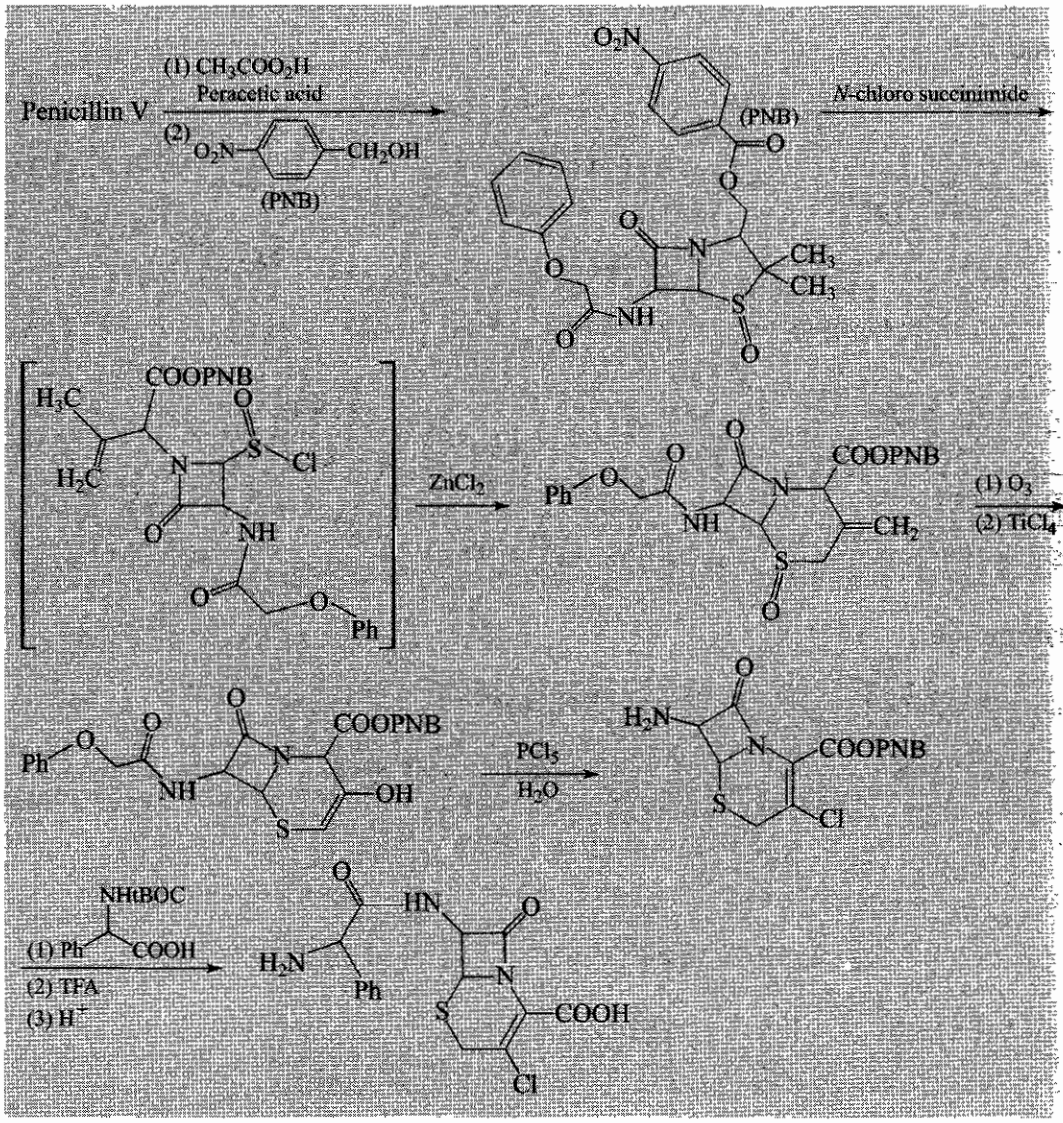
Cephradine



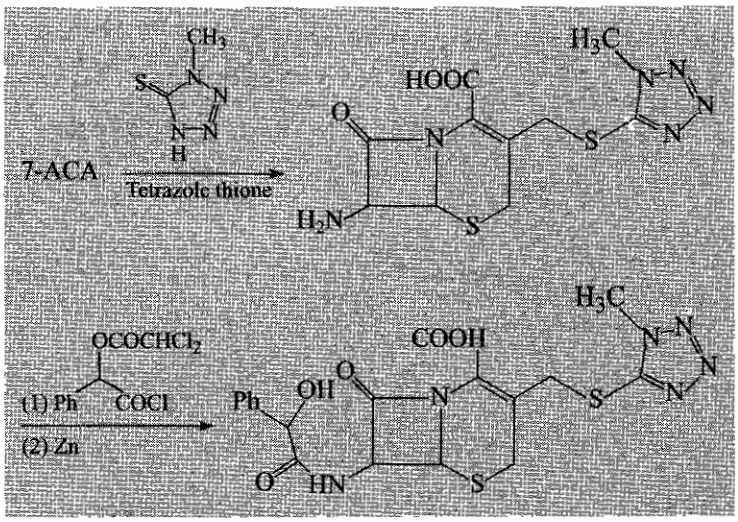
Cephalothin



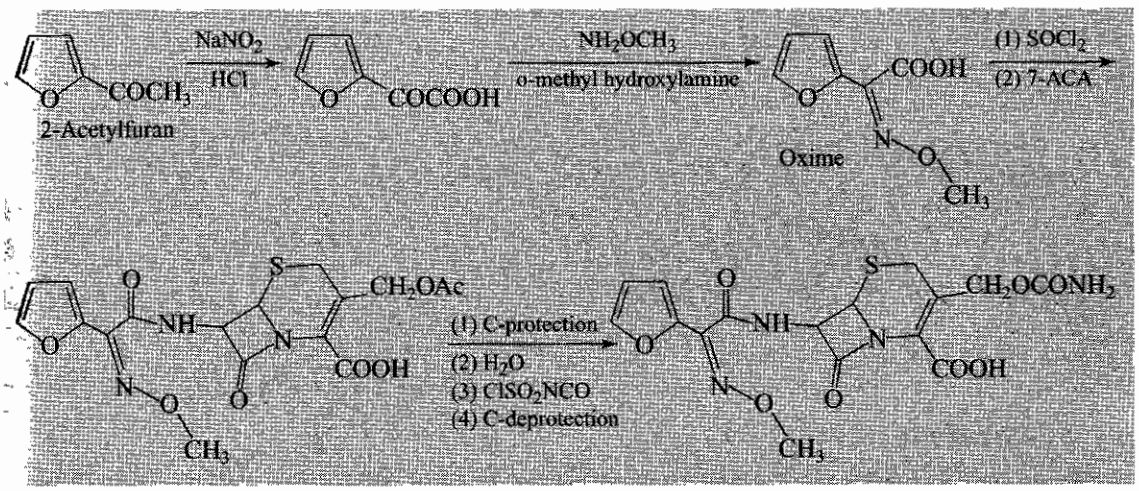
Cefaclor



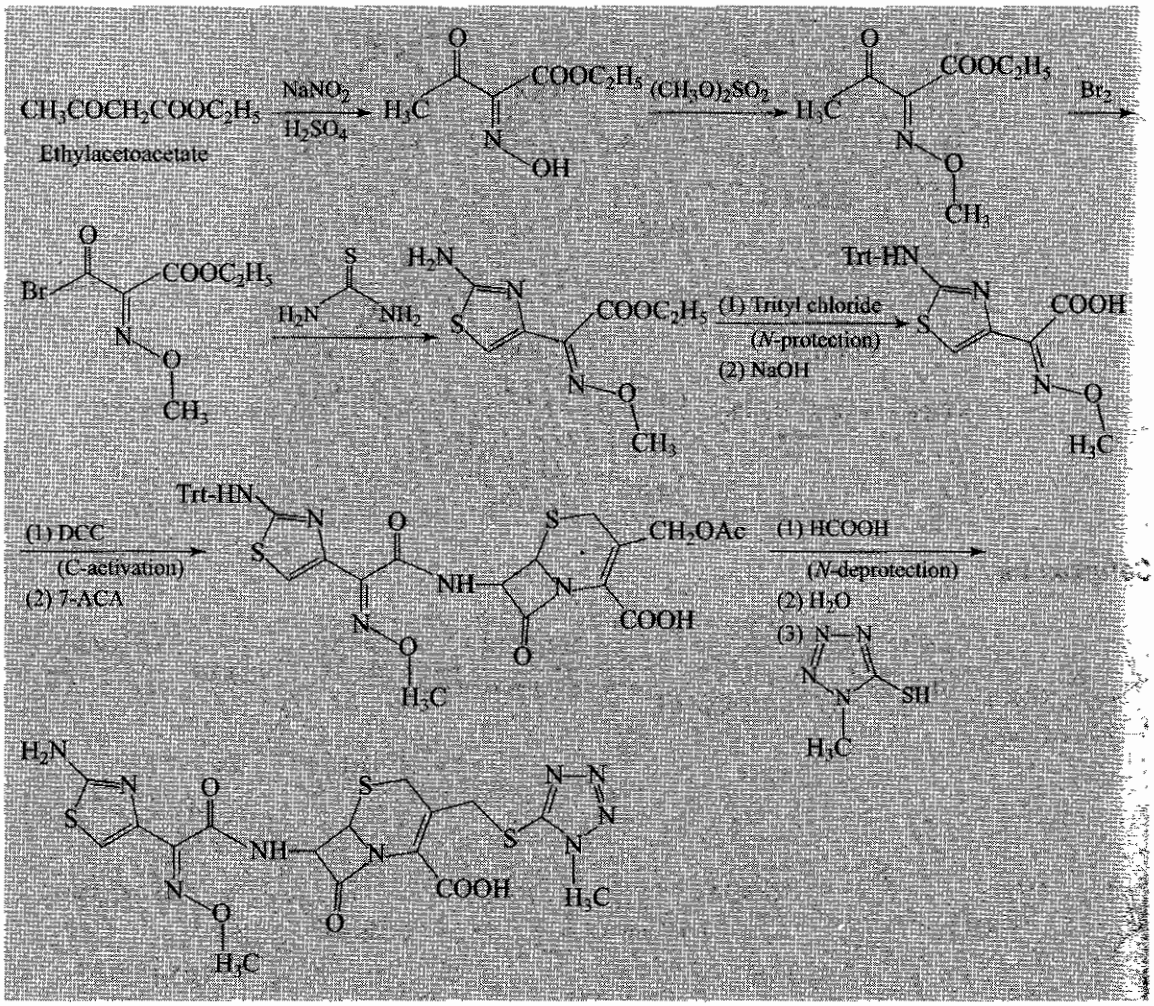
Cefamandole



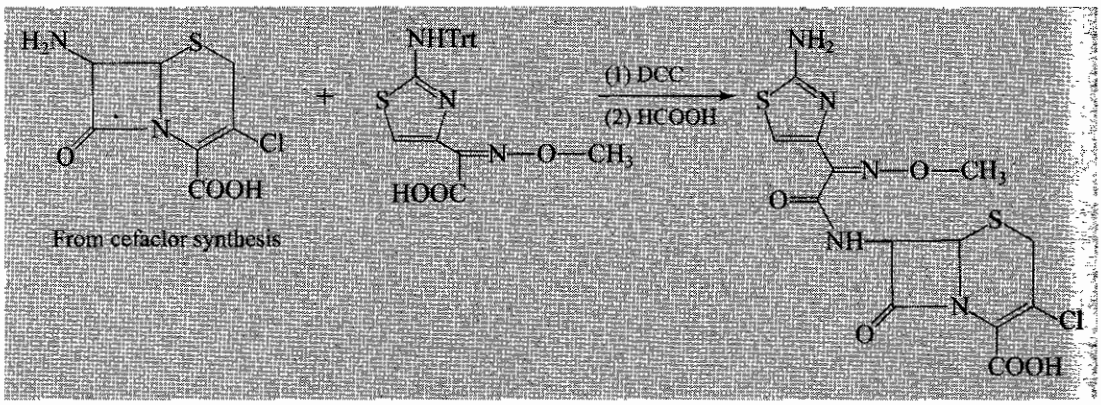
Cefuroxime



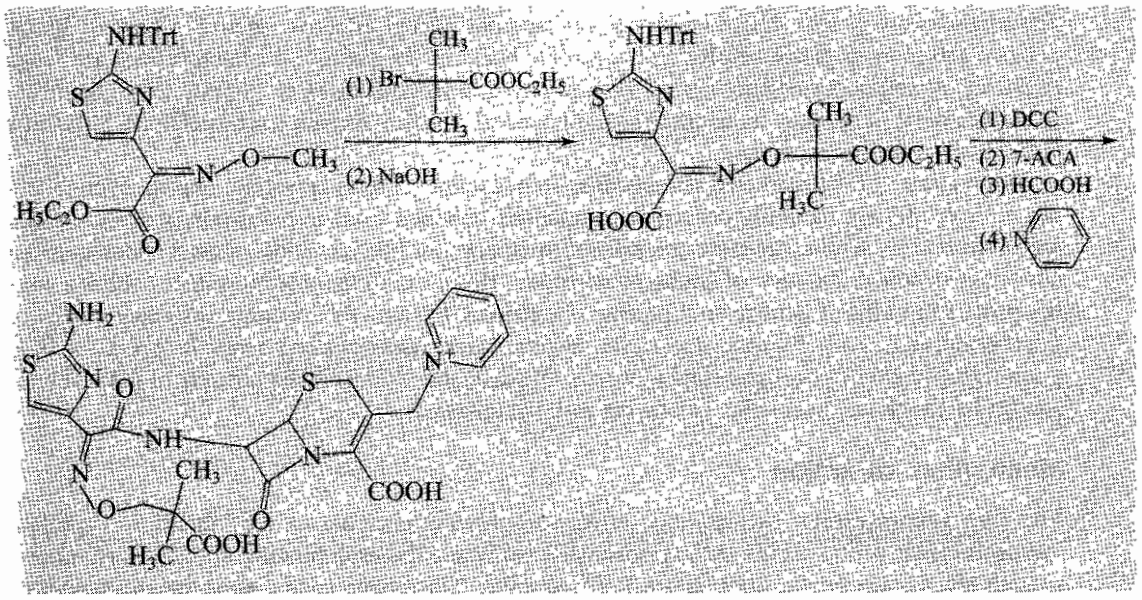
Cefotaxime



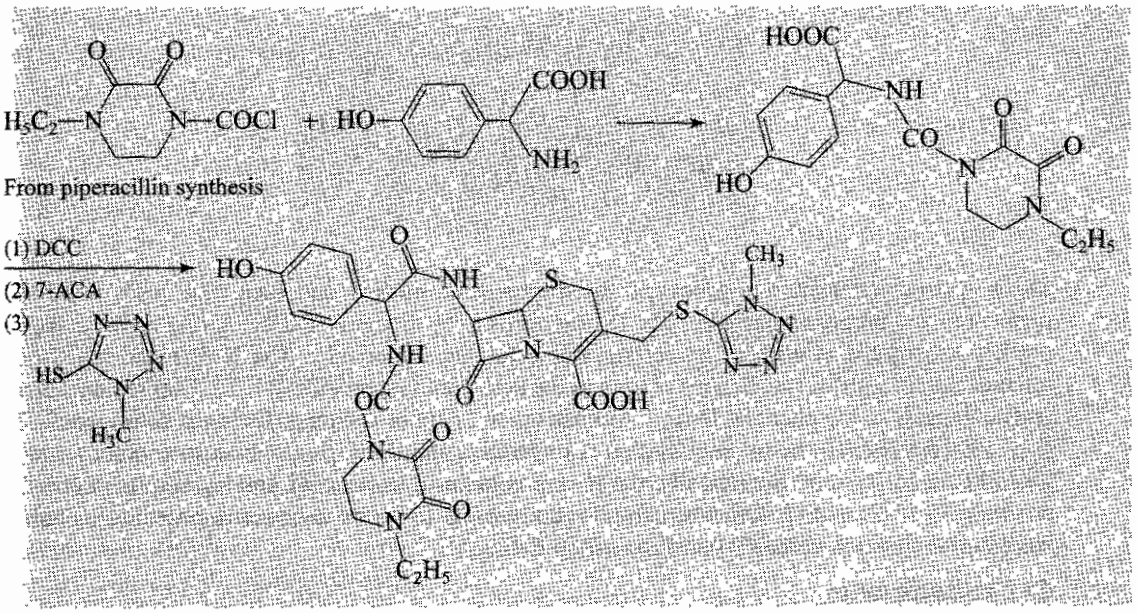
Ceftizoxime



Ceftizidime



Cefoperazone



TETRACYCLINE ANTIBIOTICS

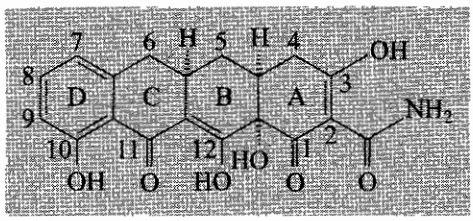
Tetracyclines are potent, broad-spectrum antibacterial agents effective against a host of gram-positive and gram-negative aerobic and anaerobic bacteria. As a result, the tetracyclines are drugs of choice or well-accepted alternatives for a variety of infectious diseases. Among these, their role in the treatment of sexually transmitted and gonococcal diseases, urinary tract infections, bronchitis and sinusitis remains prominent.

The majority of the marketed tetracyclines (tetracycline, chlortetracycline, oxytetracycline and demeclocycline) are naturally occurring compounds obtained from fermentation of *Streptomyces* spp. broths. The semi-synthetic tetracyclines (methacycline, doxycyeline, minocycline) have an advantage of longer duration of antibacterial action. However, all these tetracyclines exhibit a similar profile in terms of antibacterial potency. In general, the activity encompasses many strains of gram-negative *E. coli*, *Proteus*, *Klebsiella*, *Enterobacter*, *Niesseria* and *serratia* spp. as well as gram-negative streptococci and staphylococci. Of particular interest is the potency of tetracyclines against haemophilus, legionella, chlamydia and mycoplasma.

Mechanism of action

The tetracyclines exhibit bacteriostatic effects on growing bacteria via the inhibition of protein synthesis. Their action occurs at the ribosomal level where the drug binding to the 30S ribosomal subunit takes place on the ribosome-m-RNA complex. This phenomenon stops the attachment of amino acylated t-RNA molecules and prevents peptide chain growth.

Structural features and SAR of tetracyclines



The key structural feature is a linearly fused tetracyclic nucleus and each ring needs to be six-membered and purely carbocyclic. The D-ring needs to be aromatic and the A-ring must be appropriately substituted at each of its carbon atoms for notable activity. The B-ring and the C-ring tolerate certain substituent changes as long as the keto-enol system (at C-11, 12, 12a) remains intact and conjugated to the phenolic D-ring. Aromatisation of either D-ring or C-ring is detrimental. The D-, C, B-ring phenol-, keto-, enol-system is imperative and the A-ring must also contain a conjugated keto-enol system. Specifically, the A-ring contains a tricarbonyl derived keto-enol array at positions C-1, -2, and -3. Other structural requirements for good antibacterial activity include a basic amine function at the C-4 position of the A-ring.

C-1 substituents

The keto-enol system of the A-ring is indispensable for antibacterial activity. No variation at the C-1 position has been successful.

C-2 substituents

The carboxamide moiety is present in all naturally occurring tetracyclines and this group is crucial for antibacterial activity. The amide is best left unsubstituted or monosubstitution is acceptable in the form of activated alkylaminomethyl amide (Mannich bases). Example includes rolitetracycline. Large alkyl group on the carboxamide may alter the normal keto-enol equilibrium of the C-1, -2 and -3 conjugated system and diminishes inherent antibacterial activity. The replacement of carboxamide group or dehydration of carboxamide to the corresponding nitrile results in the loss of activity.

C-3 substituents

In conjugation with the C-1 position, the keto-enol conjugated system is imperative for antibacterial activity.

C-4 substituents

The naturally occurring tetracyclines contain α-C-4 dimethylamino substituent that favourably contributes to the keto-enolic character of the A-ring. Replacement of dimethylamino group with a hydrazone, oxime or hydroxyl group leads to a pronounced loss of activity, probably due to the increase in heteroatom basicity.

C-4a substituents

The α-hydrogen at C-4a position of tetracyclines is necessary for useful antibacterial activity.

C-5 substituents

Many naturally occurring antibacterial tetracyclines have an unsubstituted methylene moiety at the C-5 position. However, oxytetracycline contains C-5 α-hydroxyl group and was found to be a potent compound and has been modified chemically to some semisynthetic tetracyclines. Alkylation of the C-5 hydroxyl group results in a loss of activity. Ester formation is only acceptable if the free oxytetracycline can be liberated *in vivo*; only small alkyl esters are useful.

C-5a substituents

The configuration of the naturally occurring tetracyclines places the C-5a hydrogen atom in an α-configuration. Epimerisation is detrimental to antibaeterial activity.

C-6 substituents

The C-6 position is tolerant of a variety of substituents. The majority of tetracyclines have an α-methyl group and α β-hydroxyl group at this position. Demeclocyclin is a naturally occurring C-6 demethylated chlortetracycline with an excellent activity. This C-6 methyl group contributes little to the activity of tetracycline. Similarly, the C-6 hydroxyl group also appears to offer little in terms of antibacterial activity; removal of this group affords doxycycline which is a superb antibacterial.

C-7 and C-9 substituents

The nature of the aromatic D-ring predisposes the C-7 position to electrophilic substitution, and nitro and halogen groups have been introduced. Some C-7 nitro tetracyclines are among the most potent of all tetracyclines *in vitro*, but these compounds were potentially toxic/carcinogenic. Halogenated derivatives are less active. The C-7 acetoxy, azido and hydroxyl tetracyclines are inferior in terms of antibacterial activity.

C-10 substituents

The C-10 phenolic moiety is absolutely necessary for antibacterial activity.

C-11 substituents

The C-11 carbonyl moiety is part of one of the conjugated keto-enol system required for antibacterial activity.

C-11a substituents

In general, few modifications at the C-11a position of tetracycline have been tolerated. This is probably due to the detrimental effects exerted upon the keto-enol system, which is vital for magnesium cation binding and subsequent tetracycline uptake by the bacterial cell.

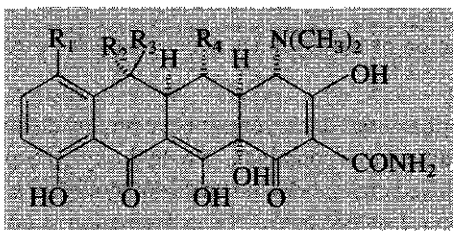
C-12 substituents

As with the C-11 position, the C-12 position is part of the keto-enol system vital for drug uptake, binding and observed antibacterial activity.

C-12a substituents

The C-12a hydroxyl group is needed for antibacterial activity although this moiety can be esterified to provide tetracycline with increased lipophilicity. Antibacterial properties are retained if the alkyl ester is small in size, and readily undergoes hydrolysis to liberate free tetracycline.

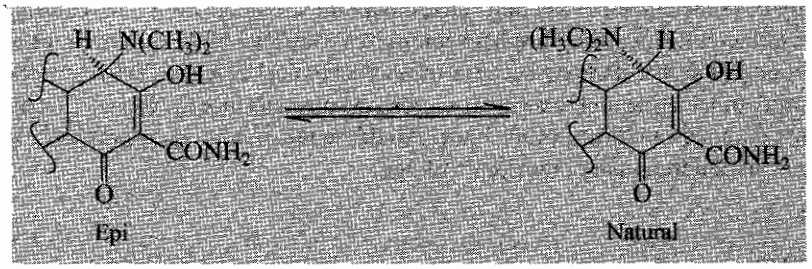
Structure of tetracyclines



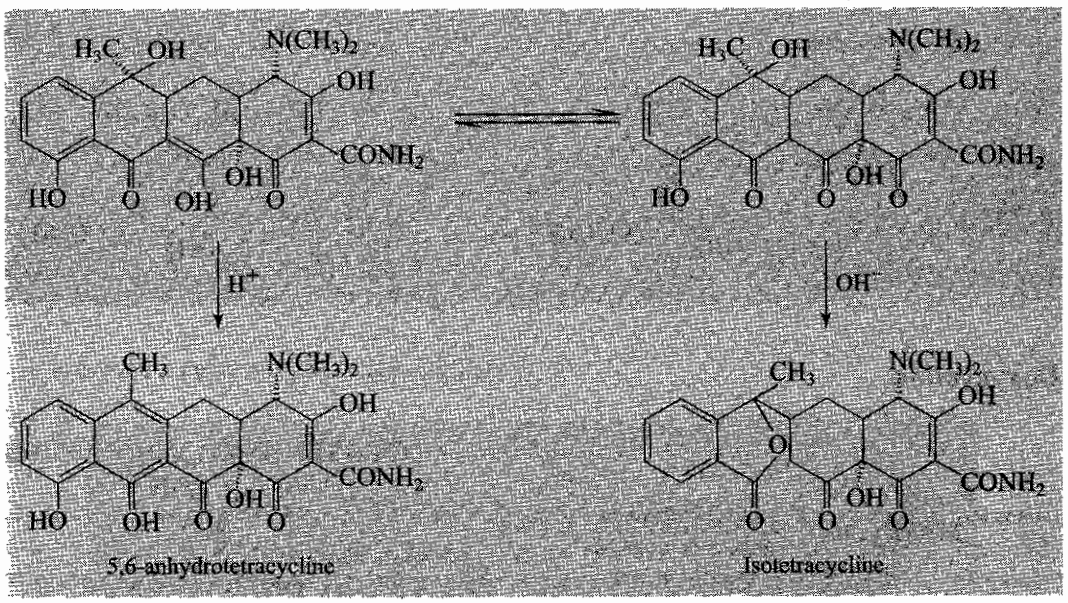
	R_1	R_2	R_3	R_4
Tetracycline	H	CH_3	OH	H
Chlortetracycline	Cl	CH_3	OH	H
Oxytetracycline	H	CH_3	OH	OH
Demeclocycline	Cl	H	OH	H
Methacycline	H	CH_2	—	OH
Doxycycline	H	H	CH_3	OH
Minocycline	$-N(CH_3)_2$	H	H	H

Effect of pH on tetracyclines

An interesting property of tetracyclines is their ability to undergo epimerisation at C-4 in solutions of intermediate pH range. These isomers are called epitetracyclines. Under the influence of the acidic conditions, an equilibrium is established in about one day consisting of approximately equal amount of isomers. Epitetraeyclines exhibit much less activity than natural isomers.



Strong acids and bases attack the tetracyclines having a hydroxyl group on C-6 causing a loss in activity through modification of C-ring. Strong acids produce dehydration through a reaction involving the C-6 hydroxyl group and C-5a hydrogen. The double bond formed between positions C-5a and C-6 induces a shift in the position of double bond between C-11a and C-12 to a position between C-11 and C-11a forming the more energetically favoured resonance of the naphthalene group found in the inactive anhydrotetracyclines.



Bases promote a reaction between the C-6 hydroxyl group and the ketone group at the C-11 position, causing the bond between the C-11 and C-11a atoms to cleave and to form the lactone ring found in the inactive isotetracycline.

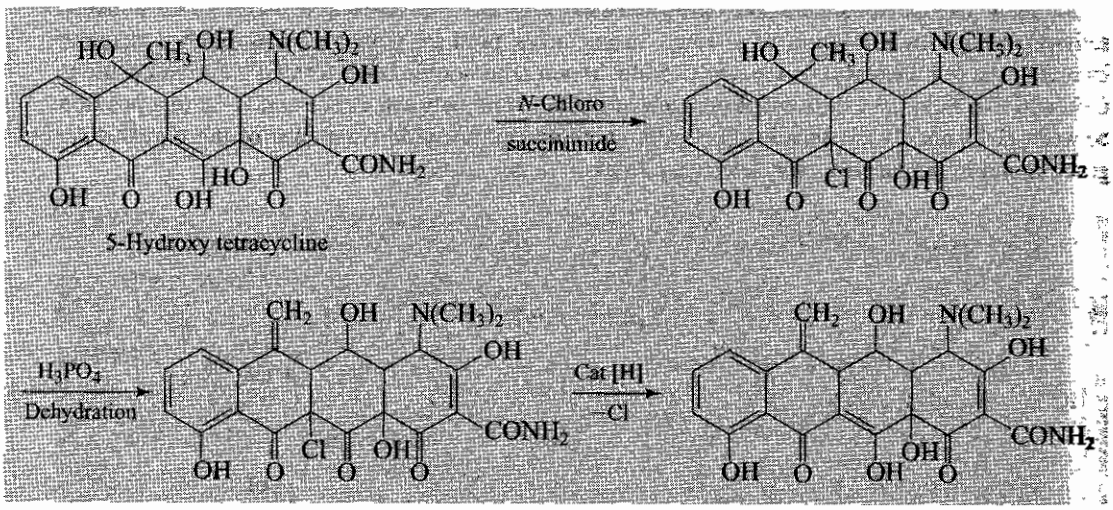
Effect of metals on tetracycline

Stable chelate complexes are formed by tetracycline with many metals, including calcium, magnesium and iron. Such chelates are insoluble in water accounting for impairment in absorption of most tetracyclines in the presence of milk, calcium, magnesium and aluminium-containing antacids and iron salts.

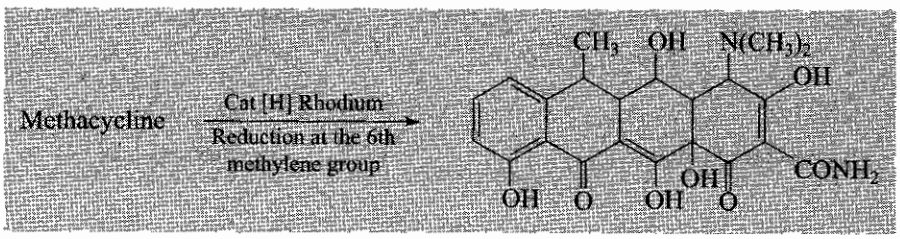
The affinity of tetracycline for calcium causes them to be laid down in newly formed bones and teeth as tetracycline-calcium orthophosphate complexes. Deposits of these antibiotics in teeth cause a yellow discolouration that darkens because of photochemical reaction. Tetracyclines are distributed into the milk of lactating mothers and also cross the placents into the foetus. The possible effect of these agents on bones and teeth of the child should be taken into consideration before their use in pregnancy or in children under eight years of age.

Synthesis

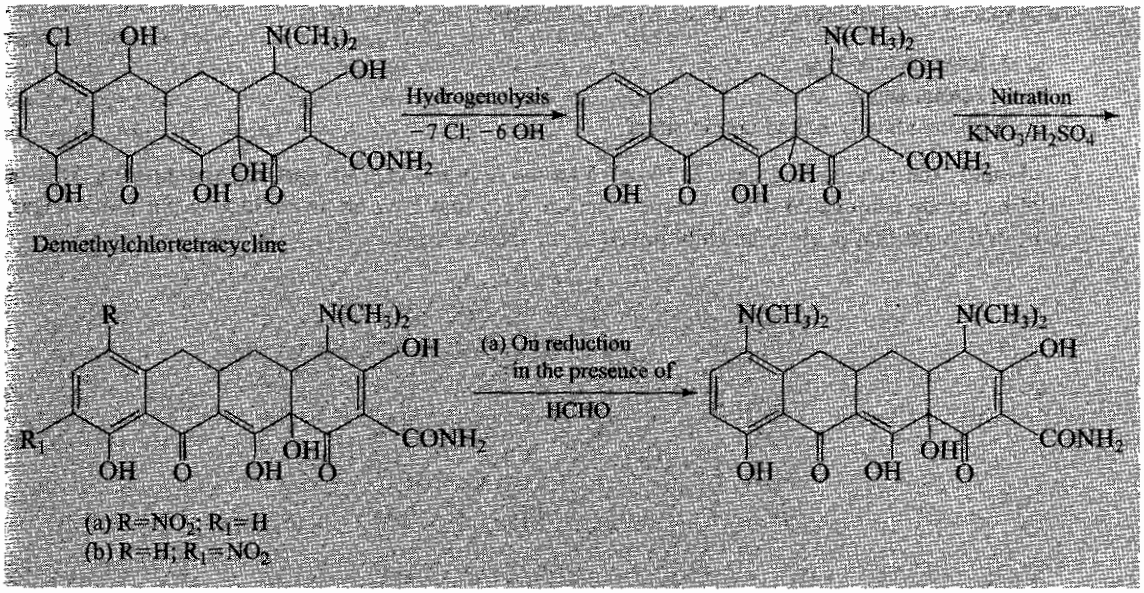
Methacycline



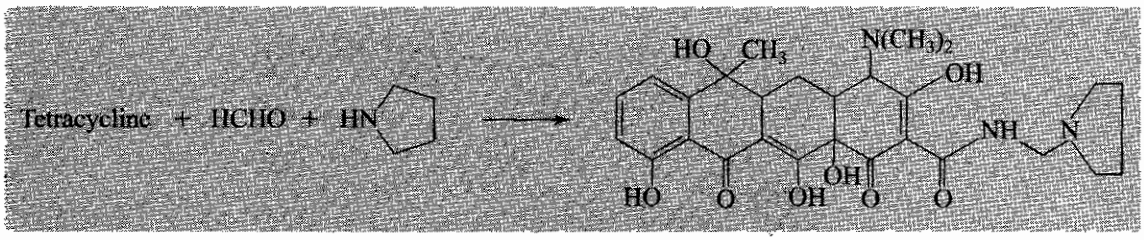
Doxycycline



Minocycline



Rolitetracycline



It is a water-soluble prodrug of tetracycline.

MACROLIDE ANTIBIOTICS

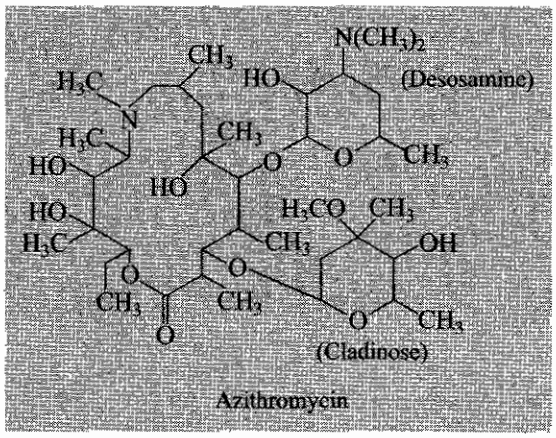
The macrolide antibacterial agents are extremely useful chemotherapeutic agents for the treatment of a variety of infectious disorders and diseases caused by a host of gram-positive bacterial pathogens. These agents as exemplified by erythromycins are generally effective against *Streptococci*, *Staphylococci*, *Chlamydia*, *Legionella* and *Mycoplasma*. As a result, the macrolides are commonly administered for respiratory, skin and tissue, and genitourinary infections caused by these pathogens.

Chemistry

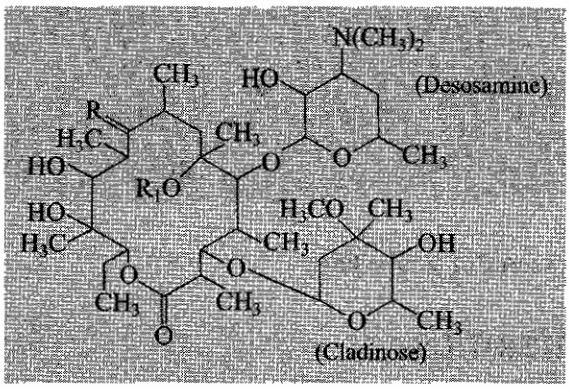
The macrolide antibiotics have three common ehemical characteristics:

a. A large lactone ring.
b. A ketone group.
c. A glycosidically linked amino sugar.

Usually the lactone ring has 12, 14 or 16 atoms in it and is often partially unsaturated, with an olefinie group conjugated with a ketone function. They may have an, in addition to the amino sugar, a neutral sugar that is glycosidically linked to the lactone ring.



Azithromycin

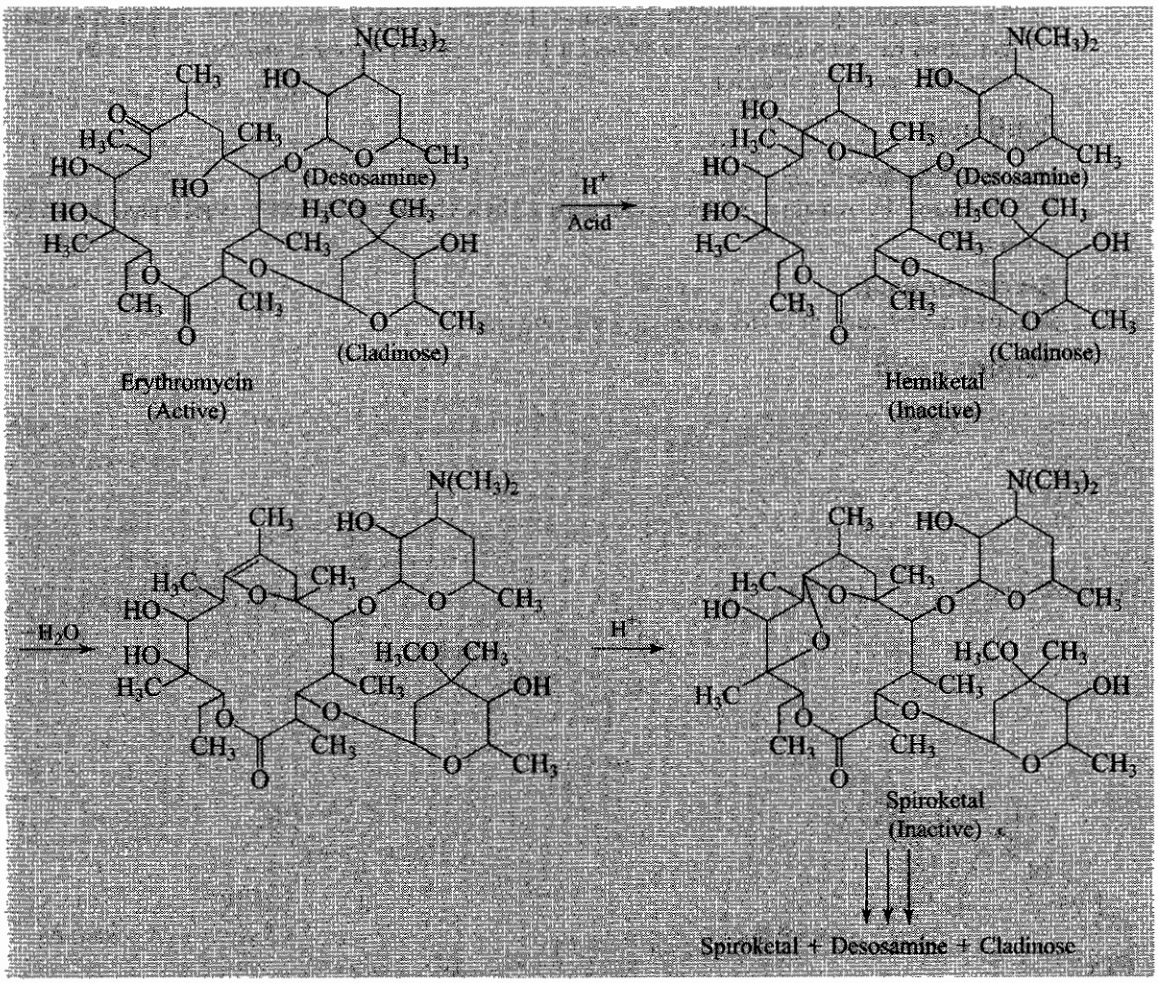


	R	R_1
Erythromycin	O	H
Roxithromyein	$CH_3OCH_2CH_2OCH_2ON=$	H
Clarithromycin	O	CH3

Mecahnism of action

The macrolides exert their antibacterial effects, which are usually bacteriostatic, via inhibition of bacterial protein biosynthesis. Specifically, the macrolides target the 50S ribosomal subunit; different members stop protein synthesis at varying stages of peptide chain elongation. The macrolides inhibit ribosomal peptidyl transferase activity. Some macrolides also inhibit the translocation of the ribosome along the mRNA template.

Acid degradation of erythromycin



Erythromycin is unstable in acid media. The C-6 hydroxyl group reversibly attacks the C-9 ketone giving rise to a hemi-ketal intermediate. Dehydration prevents regeneration of the parent erythromycin and the C-12 hydroxyl group can subsequently add to produce a spiro-ketal species. The cladinose group is cleaved from the macrocycle and more harsh conditions lead to the release of desosamine. Useful antibaeterial activity lasts upon dehydration of the hemi-ketal and the spiro-ketal is also weakly active.

SAR of Macrolide Antibiotics

1. A number of strategies have been utilised to improve the acid stability of erythromycin.
   a. The first approach involved the addition of hydroxylamine to the ketone to form oxime, e.g. roxithromycin.
   b. The second approach involves an alteration of C-6 hydroxyl group, which is the nucleophilic functionality which initiates erythromycin degradation. Modification that removes the nucleophilic nature of this hydroxyl group can retain antibacterial properties if the size of the group is kept small so as not to affect the ribosomal binding, e.g. clarithromycin.
2. The azalides (e.g. azithromycin) are semi-synthetic 15-membered congeners in which a nitrogen atom has been introduced to expand a 14-membered precursor, and this leads to an extended spectrum of action.

Synthesis

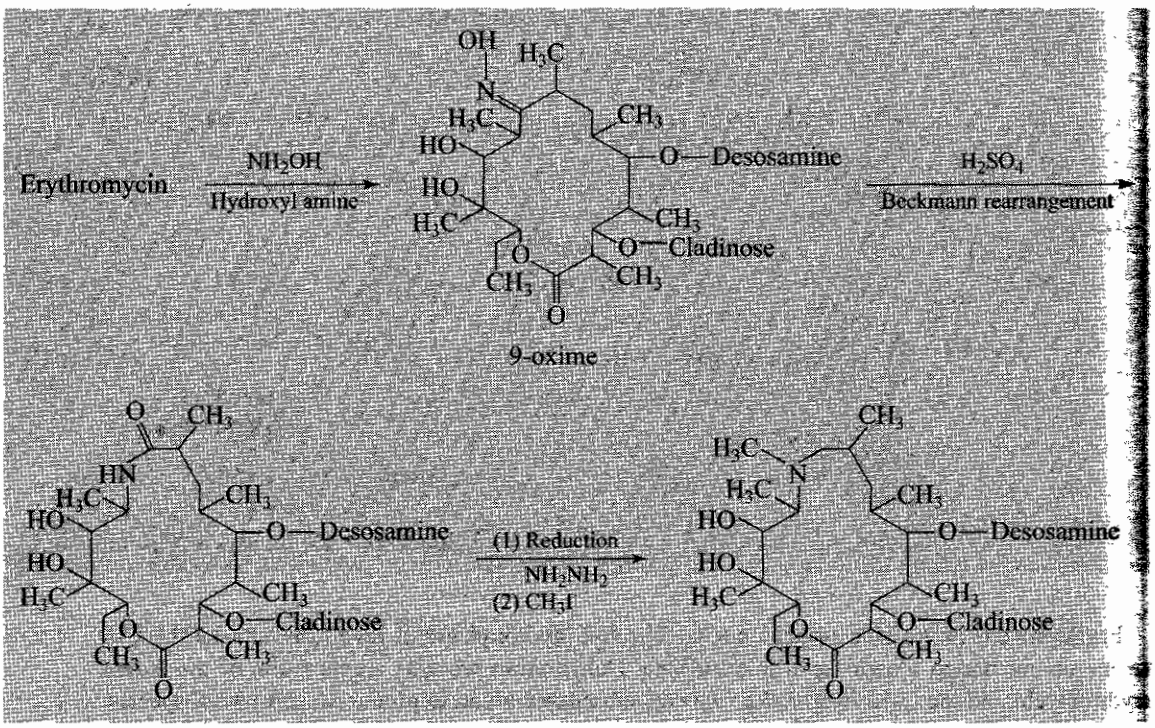
Roxithromycin

It is prepared by reacting erythromycin with $CH_3OCH_2CH_2OCH_2ONH_2$ (substituted hydroxylamine)

Clarithromycin

Selective methylation of 6-OH group of erythromycin.

Azithromycin



AMINOGLYCOSIDE ANTIBIOTICS

The aminoglycosides each contains one or more amino sugars, such as glucosamine or neosamine linked by glycosidic linkages to a basic (amino or guanidine) six-membered carbon ring. These are broad-spectrum antibiotics, in general they have greater activity against gram-negative than gram-positive bacteria.

The aminoglycosides can produce severe adverse effects, which include nephrotoxieity, ototoxicity and neuromuscular effects. These properties have limited the use of aminoglycoside chemotherapy to serious systemic indications. Some aminoglycosides can be administered for ophthalmic and topical purposes.

Mechanism of action

The aminoglycosides exhibit bactericidal effects as a result of several phenomena. Ribosomal binding and translational misreading disrupt the normal protein synthesis; cell membrane damage also plays an integral part in ensuring bacterial cell death.

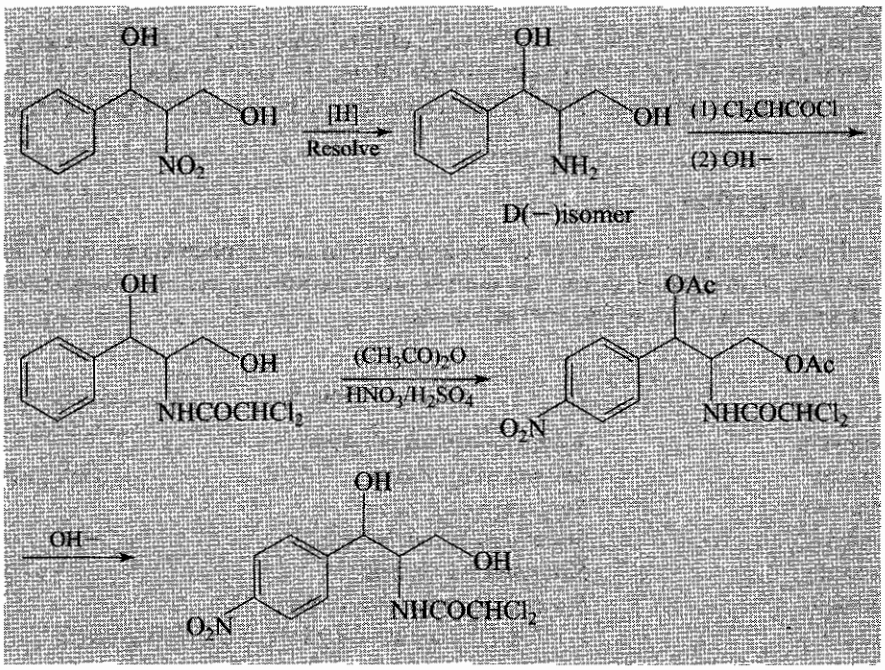
Examples:

Name	Source
1. Gentamycin	*Micromonospora purpurea*
2. Neomycin	*Streptomyces fradiae*
3. Streptomycin	*Streptomyces griseus*
4. Tobramycin	*Streptomyces tenebrarius*
5. Framycetin	*Streptomyces decaris*
6. Kanamycin	*Streptomyces kanamyceticus*
7. Amikacin	It is 1-L-(-) 4-amino-2-hydroxybutyryl kanamycin.

MISCELLANEOUS ANTIBIOTICS

Synthesis

Chloramphenicol



It is also obtained from *Streptomyces venezulae*. Because of its side effect (blood dyscrasias) and availability of safer agents, the use of this agent declined.

Bacitracin

It is a polypeptide antibiotic obtained from *Bacillus subtilis*.

Polymyxin B sulphate

It is obtained from *B. polymyxa*.

Capreomycin

It is obtained from *Streptomyces capreolus*.

Cycloserine

It is obtained from *Streptomyces orchidaceus*.

FURTHER READINGS

1. *The Journal of Antibiotics*, Japan Antibiotic Research Association, Japan.
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3. Omura, S. Ed., *Macrolide Antibiotics—Chemistry, Biology and Practice*, 2nd edition, Academic Press, **2003**.

4. Bryskier, A. and Butzler, J. P. Eds., *Antibiotics—Antibacterial and Antifungal Agents*, Blackwell Synergy Publishing, **2005**.
5. Nelson, M., Hillen, W. and Greenwald, R. A., Eds., *Tetracyclines in Biology, Chemistry and Medicine*, Birkhäuser Verlag, **2001**.

MULTIPLE-CHOICE QUESTIONS

1. Agent that acts directly on the cell membrane of the microorganisms affecting permeability is
   a. Penicillin
   b. Nystatin
   c. Tetracycline
   d. Erythromycin
2. The penicillins have a carboxylic acid group placed at
   a. C-3
   b. C-2
   c. C-6
   d. C-7
3. C-12 position is a part of the keto-enol system in
   a. Macrolide antibiotics
   b. Penicillins
   c. Tetracyclines
   d. Aminoglycoside antibioties
4. The cephalosporin antibiotic with a cyanomethyl side chain is
   a. Cephalexin
   b. Cefadroxil
   c. Cefamandole
   d. Cephacetrile
5. One of the following statements on the amino function in penicillins is False:
   a. The C-6 amine moiety is necessary for antibacterial activity
   b. Sulfonation improves antibacterial activity
   c. Acylation of the amine functionality improves activity
   d. Carboxamido derivetisation are well tolerated.
6. The naturally occurring tetracyclines contain
   a. α-C-4 dimethylamino substituent
   b. α-C-3 dimethylamino substituent
   c. α-C-3-C4 keto-enol group
   d. α-C-3 dihydroxy substituents
7. The antibiotic with an imine functionality is
   a. Ampicillin
   b. Roxithromycin
   c. Doxycycline
   d. Chloramphenicol
8. Chloramphenicol is obtained from
   a. *Streptomyces capreolus*
   b. *Streptomyces venezulae*
   c. *Streptomyces orchidaceus*
   d. *Streptomyces griseus*

9. In cephalosporins, higher resistance to hydrolysis by β-lactamases is shown when
   a. The amino group is acylated
   b. Replacement of sulphur with oxygen
   c. Oxidation of ring sulphur to sulfoxide or sulfone
   d. Introduction of C-7 α-methoxy group
10. The macrolide antibiotics do not have
   a. A large lactone ring
   b. A glycosidically linked amino sugar
   c. A spiroketal group
   d. A ketone group
11. Streptomycin is obtained from
   a. *Streptomyces capreolus*
   b. *Streptomyces venezulae*
   c. *Streptomyces orchidaceus*
   d. *Streptomyces griseus*
12. Dimethylamino substituent is present in
   a. Doxycycline
   b. Minocycline
   c. Methacycline
   d. Demeclocycline

GENERAL QUESTIONS

1. Classify Antibiotics based on their mechanism of action.
2. Give an account of Antibiotic resistyance.
3. Give the structures of various generations of penicillins and write a short note on prodrugs of penicillins.
4. Describe the SAR of tetracyclines
5. What are the important structural features of β-lactam antibiotics?
6. Write down the complete synthetic protocol for the following:
   a. Doxycycline
   b. Minocycline
   c. Cefuroxime
   d. Cephalexin
   e. Pivampicillin
   f. Dicloxacillin
   g. Roxithromycin