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Review Article

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Need and Scope of Development of β–Lactums

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Abstract

Wide range of β-lactums are still manufactured, dispensed and marketed. β- lactums have attracted the attention of physician and medicinal chemist for their versatile biological activitites. This review is an attempt to focus the study of β-lactums with their chemical additions, classifications, molecular modifications and manipulations for their extended activities. The recent growth on β-lactums are well recorded and documented in the present review.

Key words: OXA, KPC, VIM, β- lactums

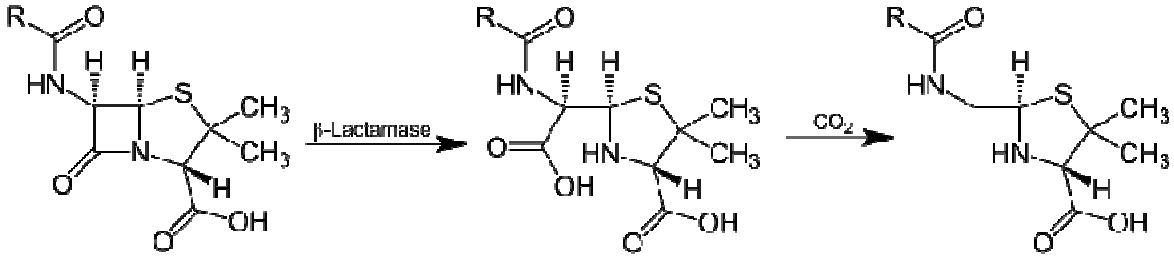
Introduction

β-lactumases are enzymes produced by bacteria of both gram+ve and gram –ve and are responsible for their resistance to β-lactum antibiotics like penicillins, cephamycins, and carbapenems (ertapenem) (Cephalosporins are relatively resistant to β-lactumase).These antibiotics have a common element in their molecular structure: a four-atom ring known as a β-lactum. The lactumase enzyme breaks that ring open, deactivating the molecule's antibacterial properties. β-lactumases are enzymes produced by pathogenic bacteria to destroy β-lactum antibiotics, such as penicillins and cephalosporins. Most cases of antibiotic resistance are caused by the presence of these secretory enzymes. β-Lactumase is an enzyme comprised of short chains of amino acids. It's most promising use is as a catalyst for the hydrolysis and aminolysis of depsipeptides. In the light of above facts it was decided to complie a review on the growth and development of new generation of β-lactums for versatile biological activities.

Penicillinase

Penicillinase is a specific type of β-lactumase, showing specificity for penicillins, again by hydrolysing the β-lactum ring. Molecular weights of the various penicillinases tend to cluster near 50 kiloDaltons.Penicillinase was the first β-lactumase to be identified: It was first isolated by Abraham and Chain in 1940 from Gram-negative E. coli even

before penicillin entered clinical use, but penicillinase production quickly spread to bacteria that previously did not produce it or produced it only rarely. Penicillinase-resistant β-lactums such as methicillin were developed, but there is now widespread resistance to even these.



Class A β-lactumases are most commonly employed by bacteria to hydrolyze various β-lactums. Although they are similar to each other at levels of primary protein sequence and tertiary structure, they behave diversely with respect to substrate specificity and activity. In order to identify the regions of the polypeptide chain containing amino acid residues that determine the specific behavior of class A enzymes, novel hybrid β-lactumase genes were previously created by Leung et al. (Protein Eng. 6, pp.66 Suppl.) using in vivo intramolecular homologous recombination. These hybrid genes have their N-terminal and C-terminal coding moieties derived respectively from the β-lactumase I (PenPC) gene of Bacillus cereus and the Bacillus licheniformis β-lactumase (PenP) gene. In this present study, five of these genes were selected for detailed analysis. The enzymes were over-expressed in an efficient Bacillus subtilis expression and secretion system and purified from the culture supernatant. The five hybrid β-lactumase enzymes studied in this project are named as Hyb 8($C^{283}L^{12}$), Hyb 7 ($C^{246}L^{49}$), Hyb 5 ($C^{212}L^{83}$), Hyb 12 ($C^{200}L^{95}$) and Hyb 6 ($C^{37}L^{258}$). For example, $C^{37}L^{258}$ indicates that out of the 295 amino acids, the first 37 are derived from β-lactumase I of B. cereus, the next 258 (residue 38-295) from the β-lactumase of B. licheniformis. According to the enzyme activity studies using penicillin G and penicillin V as substrates, the seven enzymes can be divided into two groups:

Group 1 contains the wild-type β-lactumase I (PenPC), Hyb 8, Hyb 7, Hyb 5 and Hyb 12;
Group 2 includes the wild-type B. licheniformis enzyme (PenP) and Hyb
Group 2a: Penicillinase, Molecular Class. The2a subgroup contains just penicillinases.
Group2b: Broad-Spectrum, Molecular Class A.2b Opposite to 2a, 2b is broad-spectrum β-lactumases, meaning that they are capable of inactivating penicillins and cephalosporins at the same rate. Furthermore, new subgroups were segregated from sub group 2b:

Classification of β- Lactumase
Functional Classification
Group 1
CEPHALOSPORINASE, Molecular Class C (not inhibited by clavulanic acid).Group 1 are cephalosporinases not inhibited by clavulanic acid, belonging to the molecular class C
Group 2
Group 2 are penicillinases, cephalosporinases, or both inhibited by clavulanic acid, corresponding to the molecular classes A and D reflecting the original TEM and SHV genes. However, because of the increasing number of TEM- and SHV-derived β-lactumases, they were divided into two subclasses, 2a and 2b.
2.1. Group 2be: Extended-Spectrum, Molecular Class A. Subgroup 2be, with the letter "e" for extended spectrum of activity, represents the ESBLs, which are capable of inactivating third-generation cephalosporins (ceftazidime, cefotaxime, and cefpodoxime) as well as monobactams (aztreonam).
2.2. Group 2br:
Inhibitor-Resistant, Molecular Class A (diminished inhibition by clavulanic acid).The 2br enzymes, with the letter "r" denoting reduced binding to clavulanic acid and sulbactam, are also called inhibitor-resistant TEM-derivative enzymes; nevertheless, they are commonly still susceptible to tazobactam, except where an amino acid replacement exists at position met69.
Group 2c: Carbenicillinase, Molecular Class A.Latersubgroup 2c was segregated from group 2 because these enzymes inactivate carbenicillin more than benzylpenicillin, with some effect on cloxacillin.
Group 2d: Cloxacilanase, Molecular Class D or A.Subgroup 2d enzymes inactivate cloxacillin more than benzylpenicillin, with some activity against carbenicillin; these enzymes are poorly inhibited by clavulanic acid, and

some of them are ESBLs.the correct term is "OXACILLINASE". These enzymes are able to inactivate the oxazolylpenicillins like oxacillin, cloxacillin and dicloxacillin. The enzymes belong to the molecular class D not molecular class A.

Group 2e: Cephalosporinase, Molecular Class A.Subgroup 2e enzymes are cephalosporinases that can also hydrolyse monobactams, and they are inhibited by clavulanic acid.

Group 2f: Carbapenamase, Molecular Class A.Subgroup 2f was added because these are serine-based carbapenemases, in contrast to the zinc-based carbapenemases included in group.3

Group 3

Metalloenzyme, Molecular Class B (not inhibited by clavulanic acid).Group 3 are the zinc-based or metallo {β}-lactumases, corresponding to the molecular class B, which are the only enzymes acting by the metal ion zinc. Metallo B-lactumases is able to hydrolyse penicillins, cephalosporins, and carbapenems. Thus, carbapenems are inhibited by both group 2f (serine-based mechanism) and group 3 (zinc-based mechanism)

Group 4

Penicillinase, No Molecular Class (not inhibited by clavulanic acid).Group 4 are penicillinases that are not inhibited by clavulanic acid, and they do not yet have a corresponding molecular class.

2. Molecular Classification

The molecular classification of β-lactumases is based on the nucleotide and amino acid sequences in these enzymes. To date, four classes are recognised (A-D), correlating with the functional classification. Classes A, C, and D act by a serine-based mechanism, whereas class B or metallo-β-lactumases need zinc for their action.

3. Extended-spectrum β-lactumase (ESBL)[6-13]Members of the family Enterobacteriaceae commonly express plasmid-encoded β-lactumases (e.g., TEM-1, TEM-2, and SHV-1) which confer resistance to penicillins but not to expanded-spectrum cephalosporins. In the mid-1980s, a new group of enzymes, the extended-spectrum b-lactumases (ESBLs), was detected. (First detected in Germany in 1983). ESBLs are β-lactumases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. These cephalosporins include cefotaxime, ceftriaxone and ceftazidime, as well as the oxyimino-monobactam aztreonam. Thus ESBLs confer resistance to these antibiotics and related oxyimino-β lactums. In typical circumstances, they derive from genes for TEM-1, TEM-2, or SHV-1 by mutations that alter the amino acid configuration around the active site of these β-lactumases. This extends the spectrum of β-lactum antibiotics susceptible to hydrolysis by these enzymes. An increasing number of ESBLs not of TEM or SHV lineage have recently been described. The ESBLs are frequently plasmid encoded. Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, amino glycosides). Therefore, antibiotic options in the treatment of ESBL-producing organisms are extremely limited. Carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms, yet carbapenem-resistant isolates have recently been reported. ESBL-producing organisms may appear susceptible to some extended-spectrum cephalosporins. However, treatment with such antibiotics has been associated with high failure rates.

Types

TEM β-lactumases (class A)

TEM-1 is the most commonly-encountered β-lactumase in Gram-negative bacteria. Up to 90% of ampicillin resistance in E. coli is due to the production of TEM-1. Also responsible for the ampicillin and penicillin resistance that is seen in H. influenzae and N. gonorrhoeae in increasing numbers. Although TEM-type β-lactumases are most often found in E. coli and K. pneumoniae, they are also found in other species of Gram-negative bacteria with increasing frequency. The amino acid substitutions responsible for the ESBL phenotype cluster around the active site of the enzyme and change its configuration, allowing access to oxyimino-β-lactum substrates. Opening the active site to β-lactum substrates also typically enhances the susceptibility of the enzyme to b-lactumase inhibitors, such as clavulanic acid. Single amino acid substitutions at positions 104, 164, 238, and 240 produce the ESBL phenotype, but ESBLs with the broadest spectrum usually have more than a single amino acid substitution. Based upon different combinations of changes, currently 140 TEM-type enzymes have been described. TEM-10, TEM-12, and TEM-26 are among the most common in the United States.

SHV β-lactumases (class A)

SHV-1 shares 68 percent of its amino acids with TEM-1 and has a similar overall structure. The SHV-1 β-lactumase is most commonly found in *K. pneumoniae* and is responsible for up to 20% of the plasmid-mediated ampicillin resistance in this species. ESBLs in this family also have amino acid changes around the active site, most commonly at positions 238 or 238 and 240. More than 60 SHV varieties are known. They are the predominant ESBL type in Europe and the United States and are found worldwide. SHV-5 and SHV-12 are among the most common.

CTX-M β-lactumases (class A)

These enzymes were named for their greater activity against cefotaxime than other oxyimino-β-lactum substrates (e.g., ceftazidime, ceftriaxone, or cefepime). Rather than arising by mutation, they represent examples of plasmid acquisition of β-lactumase genes normally found on the chromosome of *Kluyvera* species, a group of rarely pathogenic commensal organisms. These enzymes are not very closely related to TEM or SHV β-lactumases in that they show only approximately 40% identity with these two commonly isolated β-lactumases. More than 80 CTX-M enzymes are currently known. Despite their name, a few are more active on ceftazidime than cefotaxime. They have mainly been found in strains of *Salmonella enterica* serovar *Typhimurium* and *E. coli*, but have also been described in other species of Enterobacteriaceae and are the predominant ESBL type in parts of South America. (They are also seen in Eastern Europe) CTX-M-14, CTX-M-3, and CTX-M-2 are the most widespread. CTX-M-15 is currently (2006) the most widespread type in *E. coli* the UK and is widely prevalent in the community.

OXA β-lactumases (class D)

OXA β-lactumases were long recognized as a less common but also plasmid-mediated β-lactumase variety that could hydrolyze oxacillin and related anti-staphylococcal penicillins. These β-lactumases differ from the TEM and SHV enzymes in that they belong to molecular class D and functional group 2d. The OXA-type β-lactumases confer resistance to ampicillin and cephalothin and are characterized by their high hydrolytic activity against oxacillin and cloxacillin and the fact that they are poorly inhibited by clavulanic acid. Amino acid substitutions in OXA enzymes can also give the ESBL phenotype. While most ESBLs have been found in *E. coli*, *K. pneumoniae*, and other Enterobacteriaceae, the OXA-type ESBLs have been found mainly in *P. aeruginosa*. OXA-type ESBLs have been found mainly in *Pseudomonas aeruginosa* isolates from Turkey and France. The OXA β-lactumase family was originally created as a phenotypic rather than a genotypic group for a few β-lactumases that had a specific hydrolysis profile. Therefore, there is as little as 20% sequence homology among some of the members of this family. However, recent additions to this family show some degree of homology to one or more of the existing members of the OXA β-lactumase family. Some confer resistance predominantly to ceftazidime, but OXA-17 confers greater resistance to cefotaxime and cefepime than it does resistance to ceftazidime.

Others

Other plasmid-mediated ESBLs, such as PER, VEB, GES, and IBC β-lactumases, have been described but are uncommon and have been found mainly in *P. aeruginosa* and at a limited number of geographic sites. PER-1 in isolates in Turkey, France, and Italy; VEB-1 and VEB-2 in strains from Southeast Asia; and GES-1, GES-2, and IBC-2 in isolates from South Africa, France, and Greece. PER-1 is also common in multiresistant acinetobacter species in Korea and Turkey. Some of these enzymes are found in Enterobacteriaceae as well, whereas other uncommon ESBLs (such as BES-1, IBC-1, SFO-1, and TLA-1) have been found only in Enterobacteriaceae.

4. Inhibitor-resistant β-lactumases

Although the inhibitor-resistant β-lactumases are not ESBLs, they are often discussed with ESBLs because they are also derivatives of the classical TEM- or SHV-type enzymes. These enzymes were at first given the designation IRT for inhibitor-resistant TEM β-lactumase; however, all have subsequently been renamed with numerical TEM designations. There are at least 19 distinct inhibitor-resistant TEM β-lactumases. Inhibitor-resistant TEM β-lactumases have been found mainly in clinical isolates of *E. coli*, but also some strains of *K. pneumoniae*, *Klebsiella oxytoca*, *P. mirabilis*, and *Citrobacter freundii* .Although the inhibitor-resistant TEM variants are resistant to inhibition by clavulanic acid and sulbactam, thereby showing clinical resistance to the β-lactum lactumase inhibitor combinations of amoxicillin-clavulanate (Co-amoxiclav), ticarcillin-clavulanate, and ampicillin/sulbactam, they normally remain susceptible to inhibition by tazobactam and subsequently the combination of piperacillin/ tazobactam, although resistance has been described. To date, these β-lactumases have primarily been detected in France and a few other locations within Europe.

5. AmpC-type β-lactumases (Class C)

AmpC type β-lactumases are commonly isolated from extended-spectrum cephalosporin-resistant Gram-negative bacteria. AmpC β-lactumases (also termed class C or group 1) are typically encoded on the chromosome of many Gram-negative bacteria including *Citrobacter*, *Serratia* and *Enterobacter* species where its expression is usually inducible; it may also occur on *Escherichia coli* but is not usually inducible, although it can be hyperexpressed. AmpC type β-lactumases may also be carried on plasmids.AmpC β-lactumases, in contrast to ESBLs, hydrolyse broad and extended-spectrum cephalosporins (cephamycins as well as to oxyimino-β-lactums) but are not inhibited by β-lactumase inhibitors such as clavulanic acid.

Carbapenemases

Carbapenems are famously stable to AmpC β-lactumases and extended-spectrum-β-lactumases. Carbapenemases are a diverse group of b-lactumases that are active not only against the oxyimino-cephalosporins and cephamycins but also against the carbapenems. Aztreonam is stable to the metallo-β-lactumases, but many IMP and VIM producers are resistant, owing to other mechanisms. Carbapenemases were formerly believed to derive only from classes A, B, and D, but a class C carbapenemase has been described.

IMP-type carbapenemases (one of the metallo-β-lactumases)

Plasmid-mediated IMP-type carbapenemases, 17 varieties of which are currently known, became established in Japan in the 1990s both in enteric Gram-negative organisms and in *Pseudomonas* and *Acinetobacter* species. IMP enzymes spread slowly to other countries in the Far East, were reported from Europe in 1997, and have been found in Canada and Brazil.

VIM (Verona integron-encoded metallo-β-lactumase)

A second growing family of carbapenemases, the VIM family, was reported from Italy in 1999 and now includes 10 members, which have a wide geographic distribution in Europe, South America, and the Far East and have been found in the United States. VIM-1 was discovered in P. aeruginosa in Italy in 1996; since then, VIM-2 - now the predominant variant - was found repeatedly in Europe and the Far East; VIM-3 and -4 are minor variants of VIM-2 and -1, respectively. VIM enzymes occur mostly in P. aeruginosa, also P. putidaand, very rarely, Enterobacteriaceae. Amino acid sequence diversity is up to 10% in the VIM family, 15% in the IMP family, and 70% between VIM and IMP. Enzymes of both the families, nevertheless, are similar. Both are integron-associated, sometimes within plasmids. Both hydrolyse all β-lactums except monobactams, and evade all β-lactum inhibitors.

OXA (oxacillinase) group of β-lactumases (Class D)[15]

The OXA group of β-lactumases occurs mainly in Acinetobacter species and is divided into two clusters. OXA carbapenemases hydrolyse carbapenems very slowly *in vitro*, and the high MICs seen for some Acinetobacter hosts (>64 mg/L) may reflect secondary mechanisms. They are sometimes augmented in clinical isolates by additional resistance mechanisms, such as impermeability or efflux. OXA carbapenemases also tend to have a reduced hydrolytic efficiency towards penicillins and cephalosporins.

KPC (K. pneumoniae carbapenemase) (Class A)[17]

A few class A enzymes, most noted the plasmid-mediated KPC enzymes, are effective carbapenemases as well. Ten variants, KPC-2 through KPC-11 are known, and they are distinguished by one or two amino-acid substitutions (KPC-1 was re-sequenced in 2008 and found to be 100% homologous to published sequences of KPC-2). KPC-1 was found in North Carolina, KPC-2 in Baltimore and KPC-3 in New York. They have only 45% homology with SME and NMC/IMI enzymes and, unlike them, can be encoded by self-transmissible plasmids.The class A *Klebsiella pneumoniae* carbapenemase (KPC) is currently the most common carbapenemase, which was first detected in North Carolina, US, in 1996 and has since spread worldwide. A later publication indicated that Enterobacteriaceae that produce KPC were becoming common in the United States.

CMY (Class C)

The first class C carbapenemase was described in 2006 and was isolated from a virulent strain of *Enterobacter aerogenes*. It is carried on a plasmid, pYMG-1, and is therefore transmissible to other bacterial strains.

SME, IMI, NMC and CcrA

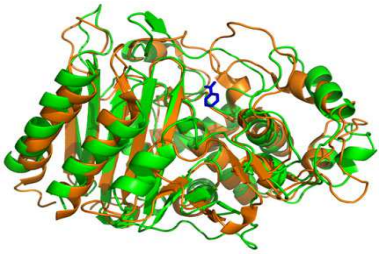
In general, these are of little clinical significance.

CcrA (CfiA). Its gene occurs in c. 1-3% of B. fragilis isolates, but fewer produce the enzyme since expression demands appropriate migration of an insertion sequence. CcrA was known before imipenem was introduced, and producers have shown little subsequent increase.

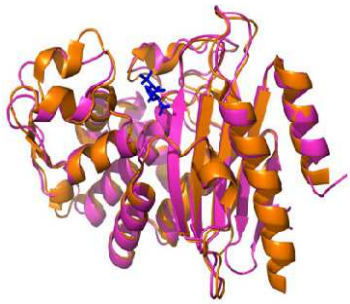
Structure of β –Lactumase

Two different β– lactumase structures have recently been determined by the Center for Structural Genomics of Infectious Diseases.

The first AmpH enzyme is from *Yersinia pestis*, the causative agent of plague, and is related to the class C (AmpC) β-lactumases, which are produced by bacteria such as Escherichia coli. Despite only 24-25% sequence homology, the structures are quite similar as can be seen by superimposing the AmpH structure (shown in orange, PDB ID:3OZH) with that of the *E. coli* Amp C structure (shown in green, PDB ID:1KDS). The Amp C structure has the inhibitor 3-nitrophenylboronic acid in its active site (depicted as a blue stick).



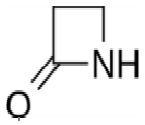
1



2

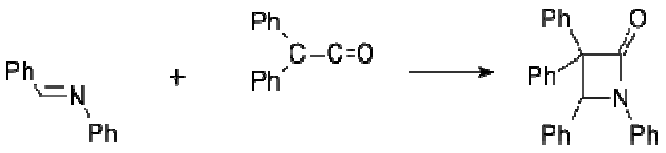
The second β-lactumase structure determined is from *Francissela tularensis*, the causative agent of tularemia. Shown in orange below, the class A enzyme (subsp. tularensis SCHUS4, PDBID:3P09), is strikingly similar to that of class A carbapenemases, which confer resistance to oxyimino-cephalosporins, cephamycins and carbapenems. It is shown superimposed on 6 alpha-(hydroxypropyl) penicillate acylated NMC-A carbapenemase structure (shown in purple, the inhibitor shown in blue, PDBID:1BUL)

Introduction of β-lactum [21-26]

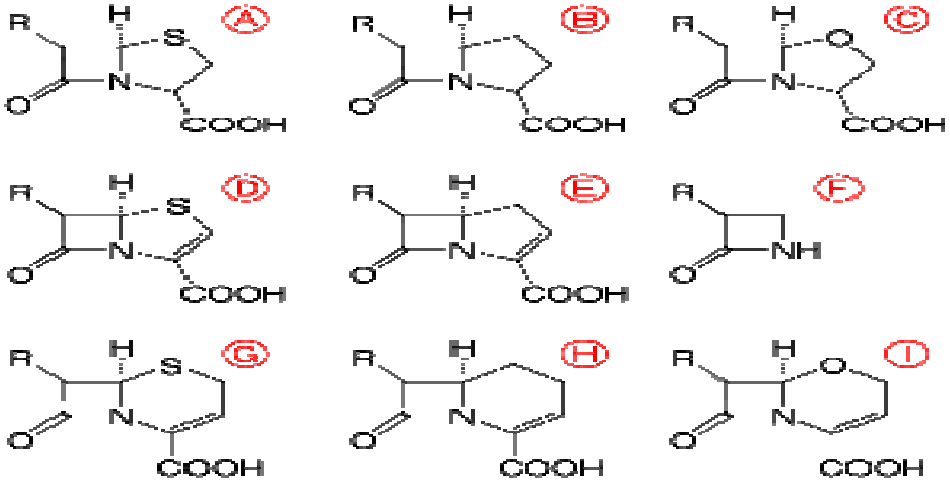


2-Azetidinone

β-Lactum antibiotics are a broad class of antibiotics, consisting of all antibiotic agents that contains a β-lactum nucleus in its molecular structure. This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems. β-Lactum antibiotics work by inhibiting cell wall synthesis by the bacterial organism and are the most widely used group of antibiotics. Bacteria often develop resistance to β-lactum antibiotics by synthesizing β-lactumase, an enzyme that attacks the β-lactum ring. To overcome this resistance, β-lactum antibiotics are often given with β-lactumase inhibitors such as clavulanic acid. A β-lactum (β-lactum) ring is a four-membered lactum. (A lactum is a cyclic amide.) It is named as such, because the nitrogen atom is attached to the β-carbon relative to the carbonyl. The simplest β-lactum possible is 2-azetidinone. The first synthetic β-lactum was prepared by Hermann Staudinger in 1907 by reaction of the Schiff base of aniline and benzaldehyde with diphenylketene in a [2+2]cycloaddition:



Nomenclature



The β-lactum core structures. (A) A penam. (B) A carbapenam. (C) An oxapenam. (D) A penem. (E) A carbapenem. (F) A monobactam. (G) A cephem. (H) A carbacephem. (I) An oxacephem.

Classification

a). β-Lactums are classified according to their core ring structures.

i. β-Lactums fused to saturated five-membered rings:

A. β-Lactums containing thiazolidine rings are named penams.
B. β-Lactums containing pyrrolidine rings are named carbapenams.
C. β-Lactums fused to oxazolidine rings are named oxapenams or clavams.

ii. β-Lactums fused to unsaturated five-membered rings:

A. β-Lactums containing 2, 3-dihydrothiazole rings are named penems.
B. β-Lactums containing 2,3-dihydro-1H-pyrrole rings are named carbapenems.

iii. β-Lactums fused to unsaturated six-membered rings:

A. β-Lactums containing 3, 6-dihydro-2H-1, 3-thiazine rings are named cephems.
B. β-Lactums containing 1, 2, 3, 4-tetrahydropyridine rings are named carbacephems.
C. β-Lactums containing 3, 6-dihydro-2H-1, 3-oxazine rings are named oxacephems.

iv. β-Lactums not fused to any other ring are named monobactams.

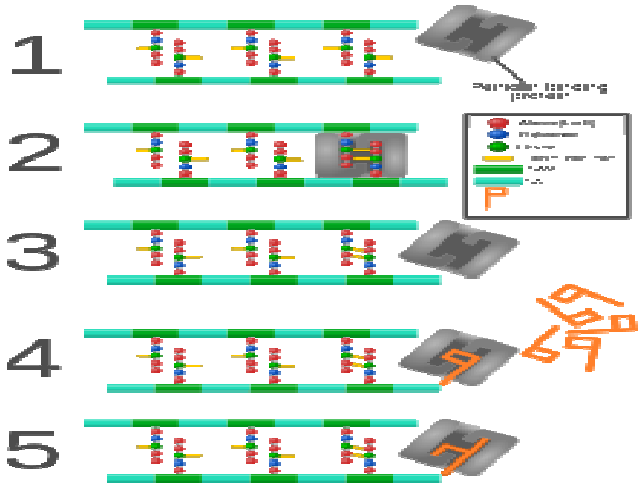
b). By convention

The bicyclic β-lactums are numbered starting with the position occupied by sulfur in the penams and cephems, regardless of which atom it is in a given class. That is, position 1 is always adjacent to the β-carbon of β-lactum ring. The numbering continues clockwise from position one until the β-carbon of β-lactum is reached, at which point numbering continues counterclockwise around the lactum ring to number the remaining to carbons. For example, the nitrogen atom of all bicyclic β-lactums fused to five-membered rings is labelled position 4, as it is in penams, while in cephems, the nitrogen is position 5. The numbering of monobactams follows that of the IUPAC; the nitrogen atom is position 1, the carbonyl carbon is 2, the α-carbon is 3, and the β-carbon 4.

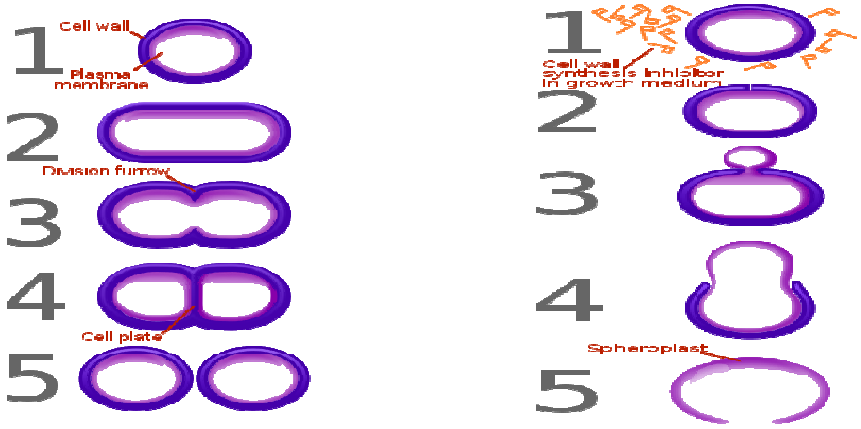
Medical Use

β-Lactum antibiotics are indicated for the prophylaxis and treatment of bacterial infections caused by susceptible organisms. At first, β-lactum antibiotics were mainly active only against Gram-positive bacteria. The recent development of broad-spectrum β-lactum antibiotics active against various Gram-negative organisms has increased their usefulness.

Mode of Action



Penicillin and other β-lactum antibiotics act by inhibiting penicillin-binding proteins, which normally catalyze cross-linking of bacterial cell walls.



In the absence of β-lactum antibiotics, the bacterial cell wall plays an important role in bacterial reproduction. Adding β-lactum antibiotics to the cell medium while bacteria are dividing will cause them to shed their cell walls and fail to divide, forming large, fragile spheroplasts. β-Lactum antibiotics are bacteriocidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). β-Lactum antibiotics block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosyntheticorganelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This is supporting the endosymbiotic theory and indicates an evolution of plastid division in land plants.

β-Lactum antibiotics are analogues of D-alanyl-D-alanine - the terminal amino acid residues on the precursor NAM/NAG-peptide subunits of the nascent peptidoglycan layer. The structural similarity between β-lactum antibiotics and D-alanyl-D-alanine facilitates their binding to the active site of penicillin-binding proteins (PBPs). The β-lactum nucleus of the molecule irreversibly binds to (acylates) the Ser_{403} residue of the PBP active site. This irreversible inhibition of the PBPs prevents the final crosslinking (transpeptidation) of the nascent peptidoglycan layer, disrupting cell wall synthesis. Under normal circumstances, peptidoglycan precursors signal a reorganisation of the bacterial cell wall and, as a consequence, trigger the activation of autolytic cell wall hydrolases. Inhibition of

cross-linkage by β-lactums causes a build-up of peptidoglycan precursors, which triggers the digestion of existing peptidoglycan by autolytic hydrolases without the production of new peptidoglycan. As a result, the bactericidal action of β-lactum antibiotics is further enhanced.

Common β-lactum antibiotics

1. Penicillins (Penams)

Semisynthetic penicillins are prepared starting from the penicillin nucleus 6-APA.

A. Narrow-spectrum:

β-lactumase sensitive

1. benzathine penicillin
2. benzylpenicillin (penicillin G)
3. phenoxymethylpenicillin (penicillin V)
4. Procaine penicillin

Penicillinase-resistant penicillins

Methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin

β-lactumase-resistant penicillins: temocillin

Moderate-spectrum:

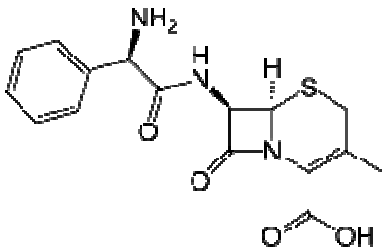
a. amoxicillin
b. ampicillin

Broad-spectrum: co-amoxiclav (amoxicillin+clavulanic acid).

Extended-spectrum: azlocillin**,** carbenicillin**,** ticarcillin**,** mezlocillin**,** piperacillin

2. Cephalosporins (Cephems)

A. First generation



Skeletal formula of cefalexin, a first-generation cephalosporin

A. Moderate spectrum

Cephalexin**,** Cephalothin**,** Cefazolin

Second generation

Moderate spectrum with anti-*Haemophilus* activity.

Cefaclor**,** Cefuroxime**,** Cefamandole

Moderate spectrum with anti-anaerobic activity.

Cefotetan, Cefoxitin

Third generation

Broad spectrum with anti-*Pseudomonas* activity.

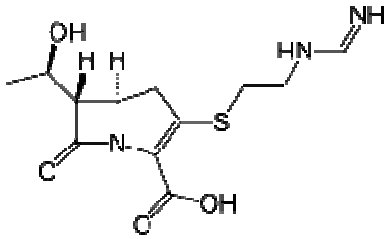
Ceftriaxone, Cefotaxime, Cefpodoximeatdox-200, Cefixime, Ceftazidime

Fourth generation

Broad spectrum with enhanced activity against Gram positive bacteria and β-lactumase stability.

Cefepime, Cefpirome

3. Carbapenems and Penems



Skeletal formula of imipenem

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Broadest spectrum of β-lactum antibiotics.

Imipenem (With Cilastatin), Meropenem, Ertapenem, Faropenem, Doripenem

4. Monobactams

Unlike other β-lactums and the monobactam contains a nucleus with no fused ring attached. Thus, there is **less probability of cross-sensitivity reactions**.

Aztreonam (Azactam)**,** Tigemonam**,** Nocardicin A**,** Tabtoxinine-B-Lactum.

Mode of Action of B-Lactum

β-Lactum antibiotics are bacteriocidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms, being the outermost and primary component of the wall. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs vary in their affinity for binding penicillin or other β-lactum antibiotics. The amount of PBPs varies among bacterial species. β-Lactum antibiotics are analogues of D-alanyl-D-alanine—the terminal amino acid residues on the precursor NAM/NAG-peptide subunits of the nascent peptidoglycan layer. The structural similarity between β-lactum antibiotics and D-alanyl-D-alanine facilitates their binding to the active site of PBPs. The β-lactum nucleus of the molecule irreversibly binds to (acylates) the Ser_{403} residue of the PBP active site. This irreversible inhibition of the PBPs prevents the final crosslinking (transpeptidation) of the nascent peptidoglycan layer, disrupting cell wall synthesis. β-Lactum antibiotics block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosyntheticorganelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This is supporting the endosymbiotic theory and indicates an evolution of plastid division in land plants.

Conclusion

β –lactums contribute a measure class of safer antibiotics. They are widely used as broad spectrum antibiotics for all the type of infections. New generation of antibiotics are predominantly preffered in clinical use. Many more newer β- lactums are expected for the clinical use and many new β- lactums are expected in future. There is a better scope, prosperity for the discovery and development of new and safer β- lactums. The structure of β- lactums, their nature, classification, chemistry to be well studied. β - lactums, their mode of action, their bacteriocidal properties and their future growth is seen with new hopes.

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