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Chemical Nomenclature of β-lactams According to the International Union of Pure and Applied Chemistry: The Case of Penicillins

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ABSTRACT :

β-lactams represent two highly important classes of antibiotics from a therapeutic perspective. First, penicillins, widely used in hospital and outpatient settings, and cephalosporins, a close analogue of the former. In addition to their therapeutic properties, penicillins hold particular chemical interest, notably the structure of the lactam ring. Beyond these widely known and studied considerations, this work aims to highlight the various elements of chemical nomenclature according to IUPAC for some penicillins. This nomenclature is complex; however, all penicillins share the same basic structure, which is 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. The difference among their analogues lies in the substituent at position 6, which is what we have attempted to elaborate on in this review.

Keywords: IUPAC nomenclature, β-lactams, Penicillins.

INTRODUCTION

Drugs belonging to the pharmacological class of β-lactams represent a widely prescribed family of antibiotics in clinical practice [1]. Beyond this significant therapeutic property, β-lactams possess diverse pharmacological potential, paving the way for novel therapeutic applications. These include LHRH antagonists [2], cholesterol absorption inhibitors [3], among others.

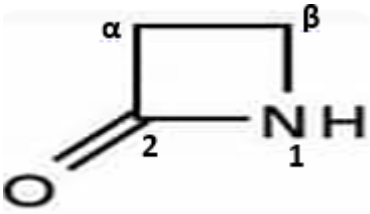
From a chemical perspective, the ring strain in the β-lactam core structure and the presence of the carbonyl group facilitate ring-opening reactions mediated by β-lactamases [4]. This unique property has been exploited for the synthesis of various medically active compounds.

Structurally, the β-lactam core is a widely occurring feature in several classes of antibiotics: cephalosporins, penicillins, carbapenems, monobactams, and carbacephems [5].

Given the chemical, structural, therapeutic, and pharmacological significance of the β-lactam ring, this review highlights the key elements of chemical nomenclature according to the International Union of Pure and Applied Chemistry [6] for the β-lactam chromophore found in penicillin-class antibiotics.

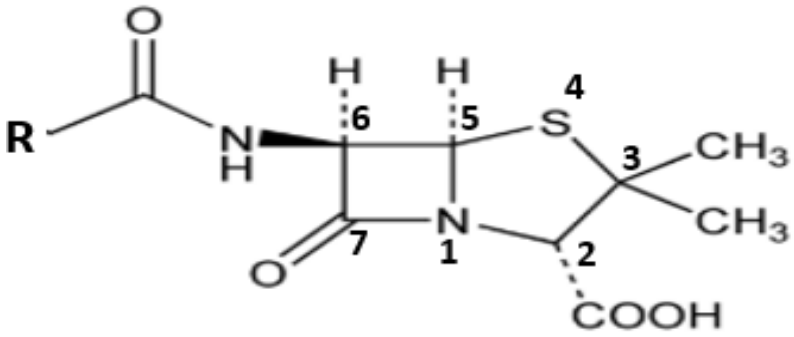
Chemical Nomenclature of Selected β-Lactam Core Penicillins

The Lactam Core



This core, also called azetidin-2-one, consists of a ketone group attached at position 2 to a four-membered heterocyclic system, one position of which is occupied by a nitrogen heteroatom. The name 'azetidin-2-one' is derived from the prefix -aza- (referring to the nitrogen), 'et' for four vertices, and the suffix -idine- (since the ring is fully saturated). Azetidine is a common name. Its IUPAC chemical name is azacyclobutan-2-one. This is an alicyclic or heterocyclic system with a 4-atom ring structure, corresponding to butane. The heteroatom is assigned the lowest position number, which is 1. The numbering direction of the ring is chosen by assigning the lowest locant to the ketone function, which determines the ring numbering sequence. The carbon adjacent to the carbonyl group is designated with the letter alpha (α), and the second carbon with the letter beta (β), hence the name β-lactam. It should be noted that other lactams exist depending on the number of carbon atoms in the ring.

The β-Lactam Core in Penicillin-Class Antibiotics



In penicillins, the β-lactam core consists of a seven-membered ring system, compared to cephalosporins which have an eight-membered ring. Clearly, this core appears to be responsible for the fusion between two rings: the thiazolidine and the β-lactam.

The penicillin core belongs to the class of bridged polycyclic heterocyclic systems. Its structure combines two rings, A and B, forming a seven-membered system that includes two heteroatoms (sulfur and nitrogen). This is a bridged system, since one of the two adjacent rings does not have at least five members—in this case, the β-lactam ring. This system is named after the open-chain hydrocarbon with the same total number of carbon atoms, prefixed by the term indicating the number of fused rings. In our case, it is bicycloheptane.

The system numbering begins by assigning the lowest locant to one of the two bridgehead atoms. Numbering continues along the longest path leading to the other bridgehead atom, then proceeds along the remaining secondary branch (or shorter bridge) back to the starting atom. In this system, the numbering sequence of atoms does not consider the position of the principal functional group or substituents.

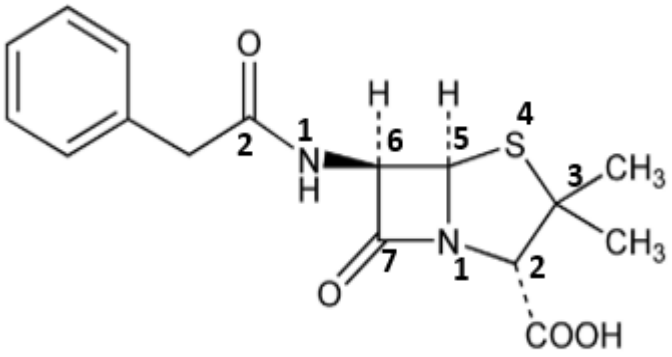
Since the system contains a heteroatom (nitrogen) at one bridgehead, this atom receives the lowest locant and is assigned position 1. The number of atoms in each bridge, including the bridgehead atoms, is specified by the corresponding numbers in brackets, listed in descending order and separated by dots (.).This yields [3.2.0], corresponding to three atoms in the major bridge, two atoms in the minor bridge, and zero atoms on the connecting bridge. The brackets are placed immediately before the hydrocarbon name, giving bicyclo[3.2.0]heptane. The latter contains a nitrogen at position 1 (denoted by "aza") and a sulfur at position 4 (denoted by "thia"). These prefixes are placed before the 'bicyclo' name, following the priority order O < S < N. The resulting nomenclature is 4-thia-1-azabicyclo[3.2.0]heptane, denoting the fundamental hydrocarbon framework.

Penicillins contain three functional groups: carboxylic acid, ketone, and amine. The carboxylic acid is the principal function and is assigned position 2: 4-thia-1-azabicyclo[3.2.0]heptan-2-carboxylic acid. The designation 'alkanoic acid' is not applied when this functional group is directly attached to a cyclic framework; it then becomes 'alkanecarboxylic acid'.

The substituents are 6-(R)amino-3,3-dimethyl-7-oxo, listed in alphabetical order of the letter: (a) for amino, (m) for dimethyl, and (o) for oxo. They are placed before the name of the main chain, while the principal functional group is always in the suffix position.

IUPAC Name of Penicillins : 6-(R)-Acylamino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

-Either the International Nonproprietary Name of Penicillin G



Principal function (P.F.): Carboxylic acid.

Parent chain : Azabicyclo[3.2.0]heptane system bearing the principal functional group at position 2, thus forming azabicyclo[3.2.0]heptane-2-carboxylic acid.

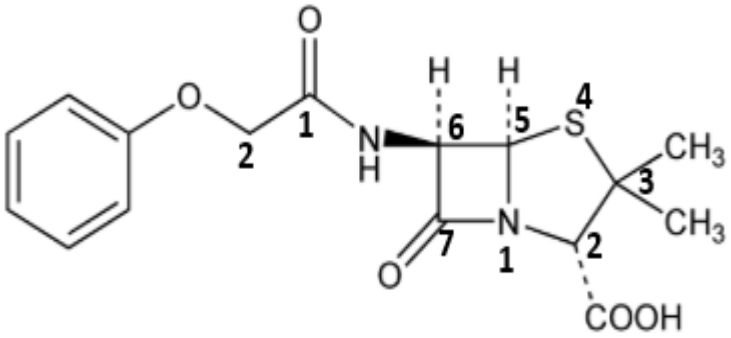
Substituents in Benzylpenicillin (Penicillin G) : The structure contains three key substituents : 3,3-dimethyl (two methyl groups at position 3), 7-oxo (ketone function at position 7) and 6-(2-phenylacetamido) (phenyl-substituted acetamide at position 6) itself substituted by a phenyl group at position 2 (2-phenylacetamido).

They are listed in alphabetical order based on the letter (m) for methyl (the prefix 'di-' is disregarded in IUPAC nomenclature), (o) for oxo, and (p) for phenylacetamido.

The substituents are ordered as follows: 3,3-dimethyl-7-oxo-6-(2-phenylacetamido). Note that for the dimethyl substituent, the final vowel (e) is dropped when followed by another vowel specifically, the (o) of 'oxo'.

Chemical Name : 3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Either the International Nonproprietary Name of Phenoxymethylpenicillin (pénicillin V).

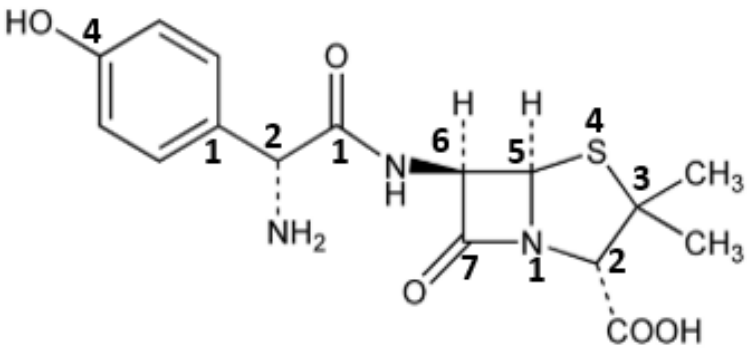


The principal functional group and parent structure are identical to those of penicillin G.

Penicillin V contains four substituents : a dimethyl group at position 3, an oxo group (ketone function) at position 7, and an acetamido group at position 6 itself substituted at position 2 by an ester group, forming a phenoxy moiety [6-(2-phenoxyacetamido)]. The alphabetical ordering remains identical for dimethyl and oxo, while phenoxyacetamido is prioritized by the letter (p). The substituents are ordered as follows: 3,3-dimethyl-7-oxo-[6-(2-phenoxyacetamido)].

Chemical Name : 6-(2-phenoxyacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

-Either the International Nonproprietary Name of Amoxicillin.

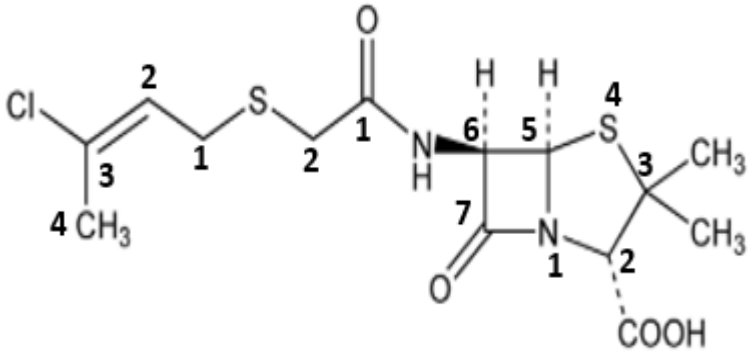


The principal functional group and parent structure are identical to those of penicillin G.

Amoxicillin contains three core substituents identical to penicillin G : 3,3-dimethyl at position 3, 7-oxo (ketone function) at position 7 and 6-acetamido at position 6 which is itself substituted at position 2 by both an amine group and a 4-hydroxyphenyl moiety. The alphabetical ordering of substituents follows IUPAC priority rules: (m) for methyl (from dimethyl), (o) for oxo, and (a) for acetamido. The latter contains two substituents that are themselves alphabetized : (a) for amino and (h) for hydroxyphenyl (where hydroxy is para-substituted on the phenyl ring), at position 6, we have 2-amino-2-(4-hydroxyphenyl)acetamido, where the terminal 'e' of 'phenyl' is dropped as it precedes a vowel ('a') from 'acetamido'. The substituents are ordered as follows : 6-[2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo.

Chemical Name : 6-(2-amino-2-(4-hydroxyphenyl)acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

-Either the International Nonproprietary Name of pénicillin S



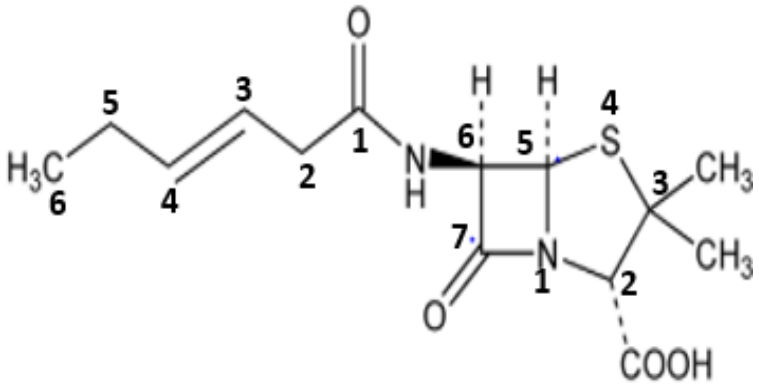
The principal functional group and parent structure correspond to the chromophore shared by all penicillins: 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Substituents: Three substituents, dimethyl group at position 3, an oxo group at position 7, and an acetamido group at position 6 (itself substituted at position 2 by a sulfanyl alkene). The alkene numbering starts from the carbon adjacent to the sulfanyl group (regardless of unsaturation or substituent position), which is the but-2-enyl group itself substituted at position 3 by chlorine. This is designated as 2-(3-chlorobut-2-enylsulfanyl)acetamide, and it is the letter (a) of 'acetamide' that determines its alphabetical priority among substituents.

The substituents are alphabetically ordered as follows : 6-[2-(3-chlorobut-2-enylsulfanyl)acetamido]-3,3-dimethyl-7-oxo.

Chemical Name : 6-[2-(3-Chlorobut-2-enylthio)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

-Either the International Nonproprietary Name of pénicilline F



The function and the main chain correspond to those of penicillin.

Substituents: There are three substituents, those common to all penicillins, Methyl groups at position 3, an oxo group at position 7, and the substituent at position 6 which differentiates it from other types of penicillins. The amine at position 6 is itself substituted with a 6-carbon alkene containing a double bond at position 3, the lowest index is given to the carbon atom adjacent to the amine group (this numbering scheme remains unaffected by the locations of double bonds or the ketone functionality), the resulting substituent is 6-hex-3-enoylamino, where the alphabetical ordering is determined by the initial letter (a) of 'acetamido' in the nomenclature. The substituents are alphabetically ordered as follows : 6-[(Hex-3-enoyl)amino]-3,3-dimethyl-7-oxo.

Chemical name : 6-[(Hex-3-enoyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Conclusion :

Although penicillin nomenclature exhibits multiple synonymous forms, the IUPAC system remains optimal as it is established by an international, multidisciplinary authority. All penicillins share a single common framework - simultaneously serving as the chromophore and foundational structure for synthesizing other penicillin derivatives. This corresponds to 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. Their structural homogeneity simplifies nomenclature. The difference lies in the substituent at position 6, which distinguishes between penicillin derivatives, whether natural or synthetic. It should be noted that this nomenclature remains incomplete; it can be refined as this review does not account for stereoisomeric elements.

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Conflict of Interest Statement:
The authors have no conflicts of interest to declare.