Cephalosporin's activity and structure: A review

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Abstract:

Cephalosporins are very important antibiotics that are used to treat various bacterial infections and are effective against a broad spectrum of anaerobic and aerobic bacteria. This mini-article and this article refer to the study of the chemical structure of the five generations of cephalosporins and the relationship of the structure to the biological activity against bacteria. Chemical modifications to the basic -lactam nucleus resulted in generations of these semi-synthetic compounds. It also greatly improved its bacterial efficacy. Substituted chemical structures at the R1 and R2 side sites on the β -lactam core are of great importance in improving the pharmacokinetic properties of compounds, as well as their solubility, stability, metabolism, and absorption.

Key words: cephalosporin, β-lactamase, anti-bacterial, penicillin-binding proteins

الخلاصة :

السيفالوسبورينات هي مضادات حيوية مهمة جدًا تستخدم لعلاج الاصابات البكتيرية المختلفة ، وهي فعالة ضد مجموعة واسعة من البكتيريا اللاهوائية والهوائية. في هذا المقال أشرنا إلى دراسة التركيب الكيميائي للأجيال الخمسة من السيفالوسبورينات وعلاقة التركيب بالنشاط البيولوجي ضد البكتيريا. أعطت التعديلات الكيميائية التي تم إجراؤها على نواة β-lactam الأساسية أجيالًا من هذه المركبات شبه المخلقة. كما أنها حسنت بشكل كبير من فعاليتها البكتيرية. التراكيب الكيميائية التي تم تعويضها في المواقع الجانبية 1R و 2R على نواة β-lactam الأساسية ، له أهمية كبيرة في تحسين الخصائص الدوائية للمركبات ، وكذلك قابليتها للذوبان ، والاستقرار ، والتمثيل الغذائي والامتصاص.

Introduction

The discovery of penicillin in 1929 and its medical use in 1940 improved our ability to treat microorganism infection [1], especially after the first use of penicillin. Advances in antimicrobial chemotherapy are made by using -lactams (cephalosporin's) compounds, which are semi-synthetic compounds (a part of the compound is produced through fermentation, and then the compound is modified through the chemical process [2]. Cephalosporium compounds (cephalosporin C) were isolated from cultures fungus *Cephalosporium acremonium* in 1948 by Giuseppe Britzu. The good efficacy and speed of treatment given by the cephalosporins made them drugs of great importance, so they were studied in detail. Cephalosporins are used in the treatment of severe infections such as urinary tract infections, skin infections, and respiratory diseases, in addition to their use in the treatment of vaginal infections [3].

The chemical structure

Cephalosporins are chemically derived from 7-aminocephalosporic acid; they are similar to penicillin in structure and action because they share a -lactam ring [3]. By substituting in positions 1, 3, and 7 on the nucleus of the cephalosporin, different compounds of cephalosporins appeared, leading to the development of 5 generations of cephalosporins. Changes in the R1 position cause changes in the compound's microbial effect; these changes typically affect the compound's stability and its effect on the -lactamase enzyme or its interference with the drug's target. Either modification to R2 lead to a change in the pharmacological properties of the compound, and modifications to R2 lead to an increase in the elimination half-life of the drug or affect the ability of the compound to reach the target site [4,5, and 6]. Figure (1) shows an example for the structure of chephalosporins. The change in the R1 position leads to changes in the microbial effect of the compound, these changes usually affect the stability of the compound and its effect on the β-lactamase enzyme.

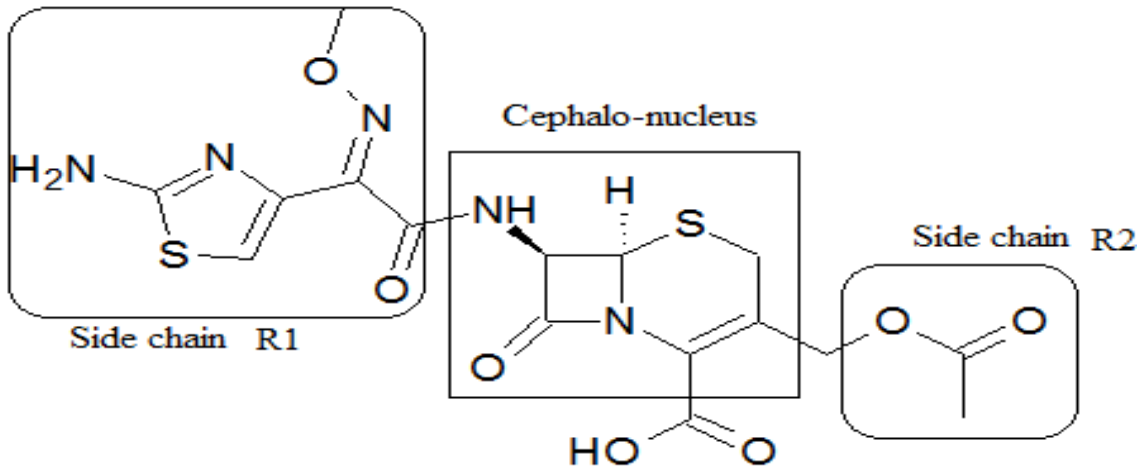

Figure (1) the nucleus formula for cephalosporins

The changes made to the R1 (C7) site include the addition of an acyl group or the replacement of a methoxy group instead of the hydrogen, as the replacement of the hydrogen leads to the development of the cephamycin group. Many chemical changes were made to the acyl side group. This modification increased resistance to -lactamase and pro-cephaloridine. The first generation of cephalosporins resulted from the addition of a thionyl or tetrazole ring to the structure at the R1 site A simple substitution of an aminobenzyl group at a site (C7) is important for the absorption of oral cephalosporins. To improve absorption in the next generation, the composition was chemically modified by producing axetil, proxetil, or esters formulation and pivoxyl esters, such as ceftamet and cefpodoxime [3, 4, 5]. The modifications to the side acyl groups at the -carbon site were the most effective chemical changes in increasing cephalosporin antibacterial activity. These modifications ranged from the simple, such as the addition of a hydroxyl group, to the complex, such as the addition of large synthetic groups. The second generation of cephalosporins is formed by combining the methoxetamine group at the -carbon site with the furyl ring on the -acyl side group [4, 6]. Many third- and fourth-generation cephalosporin compounds are the result of a methoxy-imine group being added to the -carbon site and an aminothiazole being added to the 7--acyl side chain. Alterations in the chemical structure made at R2 or site C3 play a highly important role in the

development of current cephalosporins. Figure (2) explains the generations of cephalosporins with drugs examples [7, 8]

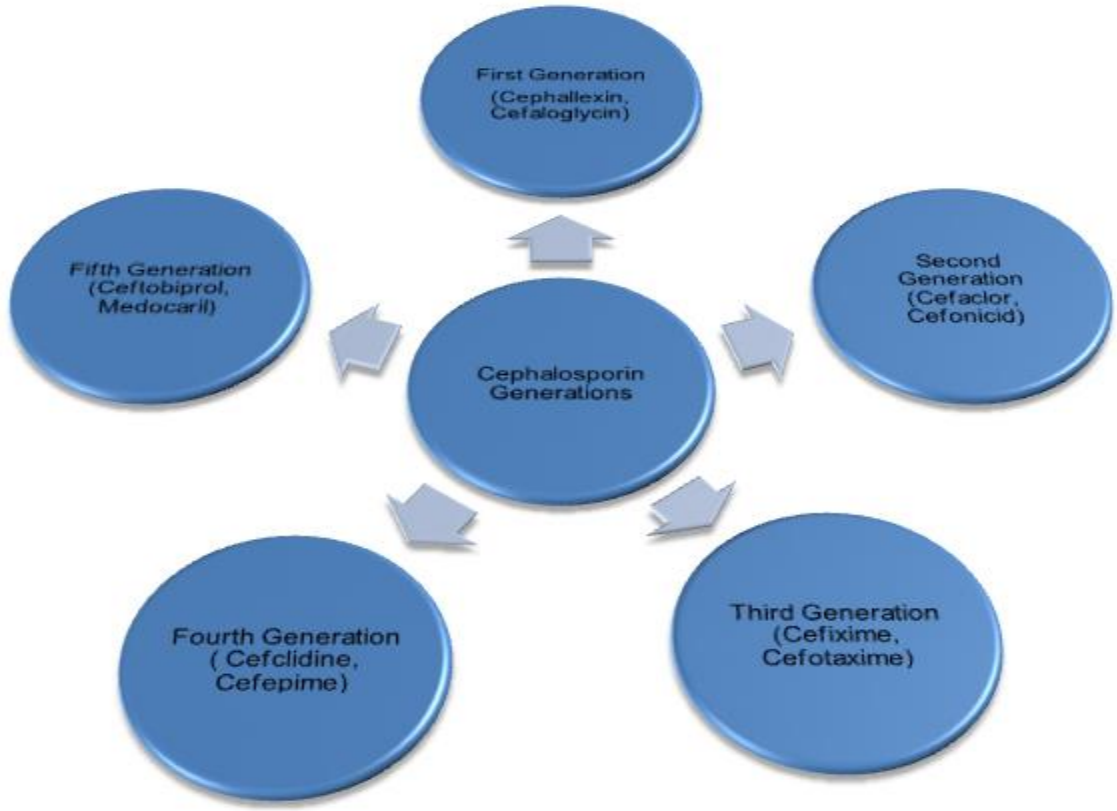

Figure (2) Generations of cephalosporins

The fifth generations of cephalosporins are represented by three compounds, namely: ceftobiprole medocaril, ceftolozan/tazobactam, and ceftaroline fosamile [9]. For ceftaroline which is N-phospho pro-drug, it depends mainly on the installation of the fourth generation cefozapran, after making modifications to sites 3 and 7, at position 3 it binbing to [4-(1-methylpyridinium-4-yl)-1,3-thiazole-2-yl]sulfanyl, and for position7 it binding to {(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazole-30yl]acetyl}amino side chain. One of its advantages is that it is more soluble in water compared to the original compound. While ceftolazane have at position 3 (5-amino-4-{[(2-aminoethyl)carbamoyl]amino}-1-methyl-1H-pyrazol-2-ium-2-yl)methyl and at position7 [(2-Z)-2-(5-amino-1,2,4-thiazol-3-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetyl]amino side chain. Ceftobiprole having at position 3(E)-[(3\R)-2-

oxo-[1, 3\-bipyrrolidin]-3-ylidene]methyl and at position 7 [(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetyl]amino side chain.

Mechanism of action of cephalosporins

Cephalosporins have three different mechanisms of action: i) binding to specific penicillin-binding proteins; ii) inhibition of cell wall synthesis; iii) activation of endogenous (self-destructive) enzymes in the bacterial cell wall. This means that cephalosporins function via their β-lactam ring, where the -lactam ring binds to the protein associated with penicillin and hinders and prevents its normal action, causing bacteria to become unable to manufacture the cell wall and die; this is due to the peptidoglycan binding to the penicillin-binding protein PBP (peptidoglycan transpeptidase) [6, 7]. There is also another mechanism to increase bacterial activity through the use of the β-lactamase enzyme. The β-lactam ring is cleaved by this enzyme, preventing it from binding to the penicillin-binding protein PBP. -lactamase inhibitors are combined with cephalosporins to increase their antibacterial activity, as in a ceftolozane/tazobactam drug. Since cephalosporin depends on its action on binding to peptidoglycan, therefore, the speed of drug effect will differ between gram-negative and positive bacteria, due to the diversity of the peptidoglycan site in the cell membrane, in addition to the speed of its diffusion in the lipopolysaccharides, as the peptidoglycan is found in the outer layer of the cell membrane of gram-positive bacteria. [9, 10]

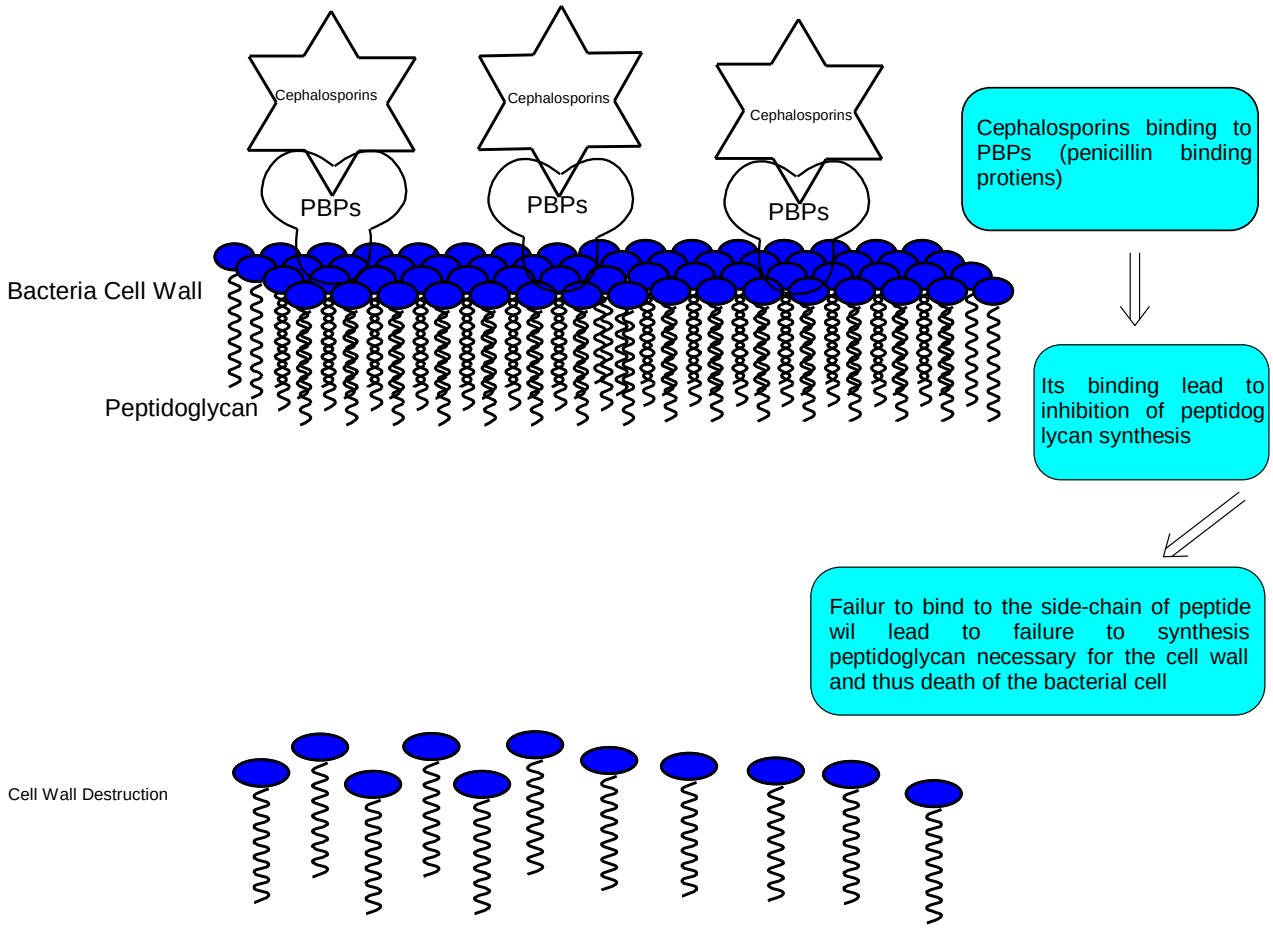

Figure (3) Schematic summarizing the mechanism of action of cephalosporins

Antibacterial activity

Cephalosporins are very important antibiotics that are used to treat various bacterial infections and are effective against a broad spectrum of anaerobic and aerobic bacteria. This is due to the difference in chemical modifications in their structures at the R1 and R2 side sites. In addition to the presence of the -lactamase ring, this is the basic nucleus in the structure, which is associated with the penicillin-associated protein and works to obstruct the construction of the cell wall in bacteria by linking to the peptidoglycan, resulting in bacterial death [9, 10, 11]. The different modifications of the position 3 and position 7 side chains improve the pharmacological properties as well as their water solubility, stability,

metabolism, -lactamase stability, absorption, and side effects in the five generations of cephalosporins. The antibacterial effectiveness of the five generations is as follows: **i)** first-generation have good activity against gram positive bacteria (*Coci.*) and moderated active against gram negative (*E.coli, Proteus, Klebsiella*) , because it is of little efficacy, it is not the best option for treatment in emergence case , **ii)** second-generation It has the same scattering of the generation before it, but it hasn't an effective trend *Pseudomonas aeruginosa*. The first and second generation are characterized by their affinity for the chemical structure of the R1 side chain, **iii)** third-generation has at C7 a 2-amino-5-thiazolyl methoximino side chain; this group stabilizes the compound towards a wide spectrum of β-lactamase inhibitors. Thus, a significant improvement in efficacy against gram-negative bacteria compared to the second generation, which is less effective, **iv)** fourth-generation, which differs from the third generation by the presence of the quaternary amine group at position C3, these compounds are considered to be zwitter ions(it has a positive sign on the nitrogen atom attached to C3 and a negative sign on the C4 of the carboxyl group), with these characteristics, the fourth generation compounds are able to penetrate the cell wall of Gram-negative bacteria(*Haemophilus influenza,S. aureus, Staphylococci, Enterobacteriaceae, Acinetobacter ssp., P. aeruginosa*) [12, 13], at a high speed, but it does not have the affinity for the beta-lactamase found in periplasmic. Pharmaceutical compounds containing the 2-amino-5-thiazolyl derivatives have a high ability to bind to PBPS in both gram-negative and gram-positive bacteria (*Penicillin-resistant strains, Pneumococci*). The fourth generation compounds are more effective than the third generation, because they are effective against *Enterobacteriaceae* , which can produce the class I of β-lactamases *in vivo*, while *in vitro* has activity against gram-negative which capable of producing AmpC-β-lactamase, **v)** fifth generation: the presence of an oxime group at C7, as well as the 1,3-thiazol ring at C3 of cefraroline, contributes to increasing the activity against Methicillin-resistant *Staphylococcus aureus* MRSA [12], the presence of the oxyimino-amino-thiazolyl ring in the main structure makes it ideal for killing *Pseudomonas Spp*. [13, 14], for ceftolozane the binding of aminothiazole ring at position C7 contributes to increasing the effectiveness of

the drug against negative bacteria, likewise, the pyrazole ring helps, when linked to a C3, to increase the stability of the compound with the β-lactamase and facilitates the passage of the compound through the outer cell wall, it gives effectiveness against *Pseudomonas aeruginosa* [15].

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