Review Article

Pharmacochemical evolution of carbapenems and structural analogues

ABSTRACT

Carbapenems are a major class of antibiotics with a β-lactam nucleus that are distinguished by their effectiveness against many resistant pathogens. The discovery of Thienamycin, from *Streptomyces cattleya*, was the starting point for these antibiotics that revolutionized the treatment of serious infections thanks to their broad spectrum and stability in the face of various β-lactamases. This work aims to describe the pharmacochemical advances of carbapenems, the structural modifications undertaken as well as their physicochemical and pharmacotherapeutic properties. A systematic review was carried out, drawing on scientific publications, specializedmanuals, and databases. Research has focused on the mechanisms of action, structural modifications, and biological properties of carbapenems, with a focus on recent innovations to improve chemical stability, broaden the antibacterial spectrum and counter bacterial resistance.Thienamycin, while promising, presented challenges for its clinical exploitation, due to its low chemical stability. This led to the synthesis of more stable semi-synthetic derivatives, such as Imipenem, the first carbapenem used in the clinic. The combination of Imipenem and Cilastatin, a dehydropeptidase-1 inhibitor, has circumvented the metabolic limitations associated with Imipenem, enhancing its therapeutic efficacy. Successive advances have given rise to other carbapenems, such as Meropenem, Doripenem, Ertapenem, Sulopenem, Faropenem, characterized by better pharmacokinetics and a broad spectrum. Their development is based on precise structural modifications, aimed at maximizing their chemical stability, bacterial efficacy while minimizing side effects and bacterial resistance. Faced with the emergence of multi-resistant pathogens, research on carbapenems remains a crucial axis. The improvement of hemi-synthesis strategies and the exploration of new therapeutic combinations open up promising prospects for combating current infectious threats.Carbapenems illustrate advances in therapeutic chemistry in the fight against resistant infections. However, the emergence of new resistances, such as those related to carbapenemases, requires constant innovation. Future generations of carbapenems will need to rely on targeted modifications to broaden their spectrum while reducing the risk of side effects.

Keywords: thienamycin, imipenem, carbapenems, thiopenemes, faropenem, pharmacochemical aspects

Introduction

β-lactam are the most widely used antibiotics in medicine because of their properties: bactericidal activity, low toxicity, few adverse effects, broad spectrum, excellent pharmacokinetic parameters and relatively low cost for certain classes[1]. In the late 1960s, the emergence of enzymes that threatened the use of β-lactam led to intensive research into β-lactamase inhibitors[2, 3]. In 1976, the first β-lactamase inhibitors, olivanic acids, were discovered. These natural bacterial products, with a "carbapenem backbone", act as broad-spectrum β-lactam[4–6]. However, their chemical instability and low cell penetration have limited their use. Subsequently, two more effective inhibitors were discovered: *S. clavuligerus*, the first clinical β-lactamase inhibitor [4–6], and thienamycin from *Streptomyces cattleya*. Thienamycin, the first carbapenem, became the model for all carbapenems, demonstrating potent broad-spectrum antibacterial activity and inhibition of β-lactamase.

Carbapenems are hospital antibiotics used for suspected multidrug-resistant bacterial infections, justified by their efficacy against third-generation cephalosporin-resistant Gram-negative bacilli. The available carbapenems are imipenem, meropenem and ertapenem, while doripenem was withdrawn from the market in 2014 [7]. The increasing use of carbapenems has led to the emergence of resistant mutants producing carbapenes, threatening the future efficacy of these treatments.

I-Thiénamycine

1) Thienamycindiscovered

The hope raised by the discovery of penicillins and cephalosporins was short-lived with the emergence of drug-resistant bacteria, which produce β-lactamases. From then on, it became urgent to develop β-lactamase inhibitors to maintain the effectiveness of β-lactam [3, 8, 9]. It was in this context that olivanic acid, the first β-lactamase inhibitor, was discovered in 1976. This one, produced by *Streptomyces clavuligerus* differs from other β-lactam known to date by a carbapenem-like structure [3, 5]. Unfortunately, olivanic acid (**Figure 1**) exhibits chemical instability and low penetration into bacterial cells, limiting its use in therapeutics[4, 10].

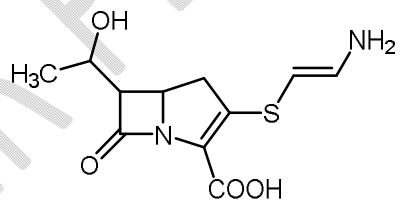


Figure 1: Chemical structure of olivanic acid

Subsequently, thienamycin, another carbapenem, was discovered during a systematic screening of the fermentation products of certain microorganisms. It was isolated from a broth of culture of a microorganism first named MA429, then *Streptomyces cattleya* following taxonomic studies that revealed that it was a new species of *Streptomyces*. In the culture broth, thienamycin was co-produced with other structurally occurring antibiotics *B*-lactam, such as penicillin *N*, cephamycin C and a derivative *N*-acetylated thienamycin [11]. Thienamycin was distinguished from other co-produced substances by its unusual antibacterial spectrum [12]. It has a broad antibacterial spectrum covering both Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*. It also has another advantage, that of being active against bacteria resistant to Penicillins and Cephalosporins[12]. Chemically, thienamycin (**Figure 2**) is characterized by a bicyclic structure, resulting from the fusion of a β-lactam ring and a dihydro-pyrrolidine ring. This bicycle carries a hydroxyethyl side chain in position 6 and a cysteamine motif in position 3.

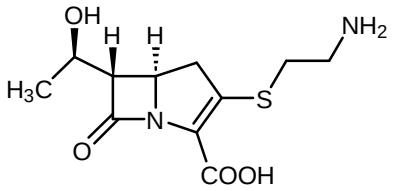


Figure 2: Chemical Structure of Thienamycin

2) Antibacterialmechanism of action

Carbapenems possess bactericidal activity by inhibiting the synthesis of peptidoglycan, an essential constituent of the bacterial wall. This inhibition results from the binding of carbapenems to enzymes essential for peptidoglycan biosynthesis. These enzymes are transpeptidases, transglycosylases, and carboxypeptidases, also known as penicillin-binding proteins (PLPs) or penicillin-fixing proteins (PFPs). Among these, transpeptidases play a crucial role in the polymerization of peptidoglycan subunits, *N*-acetyl-glucosamine (NAG) and N-acetyl-muramic acid (NAM) bound by oside bonds. Carbapenems act as a "false substrate" by binding to transpeptidases that will no longer be available for polymerization. This ability of carbapenems to bind to transpeptidases is explained by some structural analogy of the chemical structure of carbapenems with the D-alanyl-D-alanine motif located at the end of the precursor of the NAM/NAG peptide. This results in an irreversible binding between carbapenems and transpeptidases, resulting in the dissolution of peptidoglycan [13].

Carbapenems act specifically on the isoenzymes PLP1a, 1b, and 2, while other β-lactam such as penicillins and cephalosporins bind preferentially to PLP3. This results in the destruction of the bacterium without prior filamentation, unlike the inhibition of PLP3 which rather leads to the formation of long filaments before lysis. In addition, this target difference with other β-lactam leads to the release of fewer endotoxins because the inhibition of PLP1a, 1b and 2 limits the increase in bacterial biomass. This results in a reduction in the allergic risks associated with endotoxins and a lack of cross-resistance with other β-lactam[9].

3) Mechanism of bacterialresistance

Carbapenems are antibiotics with a very broad spectrum of action, so their widespread use carries a risk of selection pressure and the development of resistance. Carbapenem resistance develops through several mechanisms, which can be grouped into four main categories, namely permeability defect, overexpression of efflux pumps, target mutations, and enzymatic inactivation by carbapenemases[14–30].

- **Lack of permeability**

Carbapenems reach their targets by crossing the outer membrane of Gram-negative bacteria through specific porins. The reduction or alteration of these porins is a key mechanism of resistance. It limits the entry of the antibiotic and therefore its effectiveness. Like what *Pseudomonas aeruginosa*, is a bacterium known for the expression of low-permeability porins, which limits the action of β-lactam [14–16].

- **Overexpression of efflux pumps**

Efflux pumps actively expel antibiotics out of bacterial cells, preventing them from reaching effective concentrations. These mechanisms, often encoded by chromosomal or plasmid genes, play a key role in resistance to carbapenems in bacteria such as *Escherichia coli* and *Acinetobacter baumannii*. Mutations that increase the expression of genes linked to efflux pumps aggravate this phenomenon [17–19].

- **Target Mutations**

Bacteria can develop genetic mutations that alter the binding sites of carbapenems. Mutations in penicillin-binding proteins or the acquisition of mosaic genes confer increased resistance. This mechanism is well illustrated in β-lactam resistances in *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* [20, 21].

- **Enzyme inactivation by carbapenemases**

This is the main mechanism of resistance to carbapenems, especially in Enterobacteriaceae, is enzymatic inactivation by carbapenemases[30]. This form of resistance is mainly encoded by plasmids, which makes them highly transferable to enterobacteriaceae, and therefore potentially responsible for epidemics. It is widely associated with multidrug resistance in bacteria. The enzymes that hydrolyze carbapenems or carbapenemases are divided into four main classes according to the Ambler classification [28, 29].

- Ambler's Class A beta-lactamases

Ambler's Class A beta-lactamases, also known as penicillinases, are enzymes produced by certain bacteria to hydrolyze the beta-lactam nucleus of antibiotics. This group mainly includes penicillinases and *Klebsiella pneumoniae* carbapenemase (KPC). These enzymes possess a broad spectrum of activity similar to that of extended-spectrum s β-lactamases, with extensive activity vis-à-vis carbapenems. Their activity is inhibited in vitro by clinically available beta-lactamase inhibitors such as clavulanic acid, tazobactam and avibactam [26, 27].

- Ambler's Class B beta-lactamases

Ambler Class B beta-lactamases, also known as metallo beta-lactamases (MBLs), are enzymes characterized by their dependence on metal ions (zinc), for their catalytic activity. Unlike other classes, they hydrolyze a wide range of beta-lactam antibiotics, including carbapenems, but not monobactams. These enzymes are often associated with multidrug-resistant bacteria, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and certain enterobacteriaceae. Their expression poses a major threat in the clinic, as there are currently no specific commercially available inhibitors to counter their action, limiting therapeutic options [24, 25]

- Ambler's Class C beta-lactamases

Ambler's Class C beta-lactamases, also known as cephalosporinases, primarily hydrolyze cephalosporins, but they exhibit low intrinsic activity against carbapenems. Under certain conditions, such as an overproduction of these enzymes or in the presence of porin changes in Gram-negative bacteria (reducing the entry of antibiotics), their impact on carbapenems can be amplified. These combined mechanisms are of particular concern in pathogens such as *Enterobacter cloacae* or *Pseudomonas aeruginosa*, where they contribute to increased resistance, making treatments for severe infections even more complex [24, 25].

- Ambler's D-class beta-lactamases

Ambler's D-class beta-lactamases, also known as oxacillinases (OXAs), are various enzymes capable of hydrolyzing penicillins and, in some cases, carbapenems. They are distinguished by their low affinity for classical beta-lactamase inhibitors. Oxacillinases carbapenemases, such as OXA-23, OXA-48 or OXA-58, are of particular concern in the clinic, as they confer resistance to carbapenems, often used as antibiotics of last resort. These enzymes are mainly found in Gram-negative bacteria such as *Acinetobacter baumannii* or certain *Enterobacteriaceae*, and their spread, facilitated by plasmids, poses a major threat to the treatment of nosocomial infections [22, 23].

4) Limitations of use of Thienamycin

Thienamycin, although effective, has never been used therapeutically, due to its chemical instability in basic aqueous solution, where it undergoes hydrolysis when the pH of the solution is above 8 [31, 32]. In addition, Thienamycin is highly susceptible to nucleophilic attack, so the amine function of the cysteamine chain of a first

molecule can react with the carbonyl of the β-lactam ring of a second molecule to lead to inactive dimers (**Figure 3**).

This dimerization phenomenon, which is the consequence of an over-reactivity of thienamycin, leads to an opening of the β-lactam nucleus, which is essential for the antibacterial activities of the molecule [31, 32]. Because of this chemical instability but its remarkable antibacterial activity against Gram-negative bacteria, Thienamycin has served as a basic model for the development of carbapenems used in therapeutics[33].

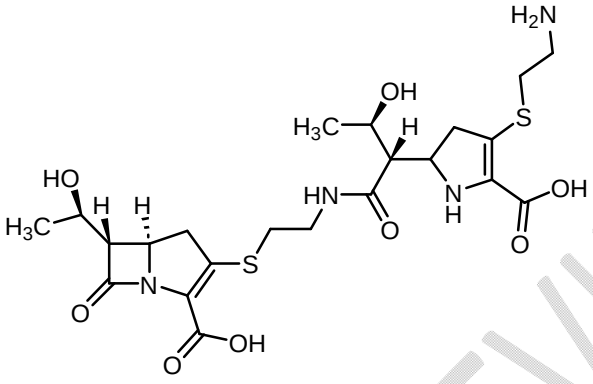


Figure 3: Chemical structure of a thienamycin dimer

Thus, in order to overcome its drawbacks of use, pharmacomodulation studies have been conducted around Thienamycin, with the aim of obtaining new molecules with more stability and performance. The pharmacomodulationsundertakenaroundThienamycinhadseveral objectives, namely:

- Increase the chemical stability of the molecule
- Improve pharmacokinetic parameters, including half-life time
- Expand theantibacterialspectrum
- Fightagainstbacterialresistance.

To carry out these pharmacomodulations, structure-activity relationship (SAR) studies were undertaken to identify the structural elements essential for the maintenance of antibacterial activity. Thesefoundthat:

5) Study of structure-activityrelationships

Studies of structure-activity relationships (SARs) have established that:

- The bicycle carbapenem nucleus is the pharmacophore vector, its integrity is essential to induce antibacterial activity. Any opening of the β-lactam leads to a loss of activity. In addition, the presence of the carboxylic acid function is essential for the recognition and interaction with the biological target[34].
- The hydroxyethyl group at position 6, in the R/S configuration (Trans configuration of carbons 5 and 6) confers to thienamycin a high resistance to extended-spectrum β-lactamases (ESBLs). In addition, the hydroxyethyl chain relatively smaller than the acylamine chain of penicillins, combined with the zwitterionic charge state, allows carbapenems to better pass through the porins of the outer membranes of Gram-negative bacteria[13, 35].
- The stereochemistry of carbon atoms is important, particularly that of carbons 5 and 6, because it allows the molecule to adopt the configuration or spatial arrangement necessary to mimic the natural substrates of Penicillin-Fixing Proteins (PLPs)[34].
- The cysteamine chain at position 3 does not seem to be indispensable but it influences The expanse of the antibacterial spectrum because of its basic character. In addition, due to the presence of the terminal amine function, it constitutes a site of inactivation of the molecule by the formation of dimer[35].

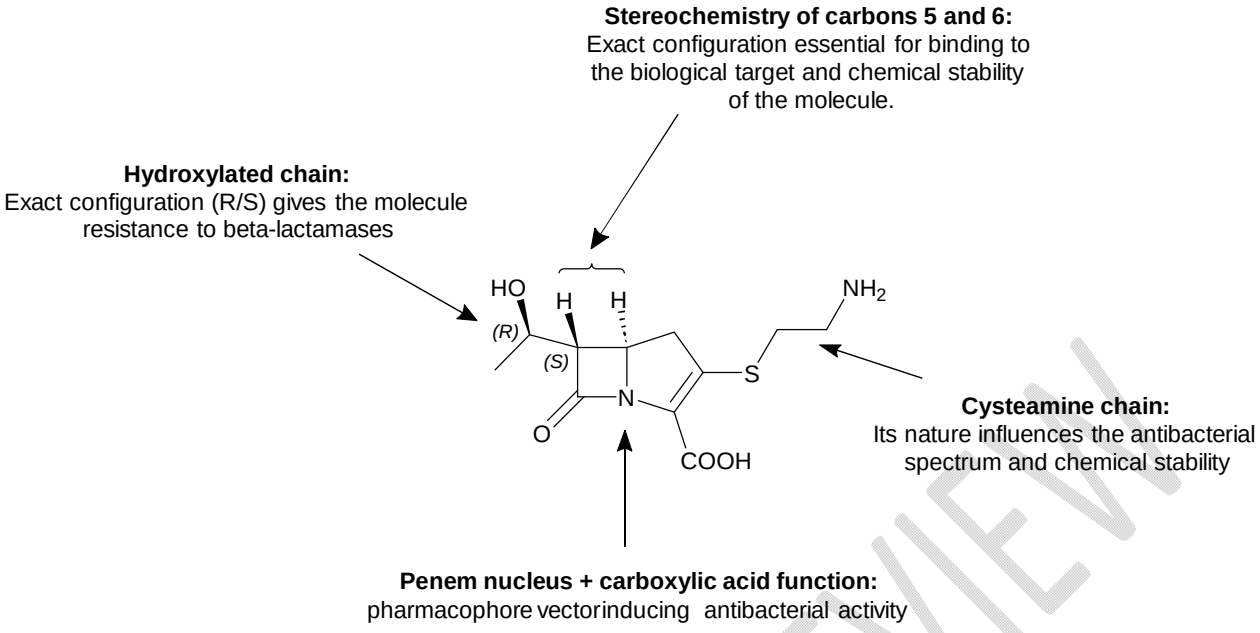


Figure 4: Structural elements essential for maintaining antibacterial activity.

The good knowledge of the structure-activity relationships of thienamycin has made it possible to undertake several pharmacomodulation strategies, particularly on the cysteamine chain and carbon at position 4. These chemical variations led to the hemisynthetic derivatives of Thienamycin.

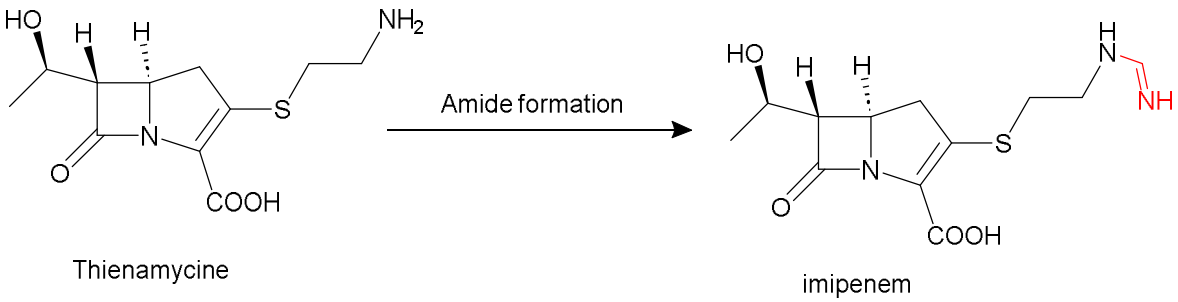
II-Hemisynthetic derivatives of thienamycin

1) Chemical modulation of the cysteamine chain at position 1

This first pharmacomodulation strategy undertaken around Thienamycin was intended to increase the chemical stability of the molecule by reducing the chemical reactivity of the terminal amine function of cysteamine. This molecule, which is involved in dimerization phenomena, is responsible for the inactivation of the molecule in a biological environment[34].

- **Transformation of cysteamine amine into amidine**

This first pharmacomodulation strategy undertaken around Thienamycin was intended to increase the chemical stability of the molecule by reducing the chemical reactivity of the terminal amine function of cysteamine. This molecule, which is involved in dimerization phenomena, is responsible for the inactivation of the molecule in a biological environment. To avoid this phenomenon, the amine function of cysteamine has been transformed into the amidine function to lead to the formylimidoylthiénamycine[28, 36]. The latter, which is chemically more stable than Thienamycin, will be called Imipenem (**Figure 5**). Imipenem has an antibacterial spectrum of activity identical to that of thienamycin with a spectrum that covers Gram-negative bacilli such as *Pseudomonas aeruginosa*, Gram-positive cocci of which *Enterococcus faecalis* and on anaerobes.



Thienamycine imipenem

Figure 5: Amidination of the terminal amine of cysteamine

Clinical use of Imipenem has shown low urinary and plasma concentrations due to excessive metabolism of DHP-1 in the kidneys. This enzyme was identified in 1982 by Kropp, who showed that plasma concentrations of Imipenem were little influenced in rabbits and rats that underwent renal artery ligation[28, 36]. To obtain satisfactory urinary and plasma concentrations, Imipenem must Be a partner to the Cilastatin, an inhibitor competitive selection of the DHP-1. The pharmacokinetic studies carried out showed that a 1:1 ratio of Imipenem and Cilastatin was essential to ensure good efficacy of the combination. In addition, other studies have shown that Imipenem exhibits tubular nephrotoxicity when used alone. It appears that Cilastatin plays a dual role in this association, namely the inhibition of DHP-1 and the prevention of nephrotoxicity[28, 36]. The Imipenem having Presented nephrotoxicity and low plasma concentrations requiring its association with Cilastatin. The combination of imipenem-cilastatin (**Figure 6**), Marketed under the name of Tienam®, was Authorized par la Food and Drug Administration (FDA) en 1985[28, 36].

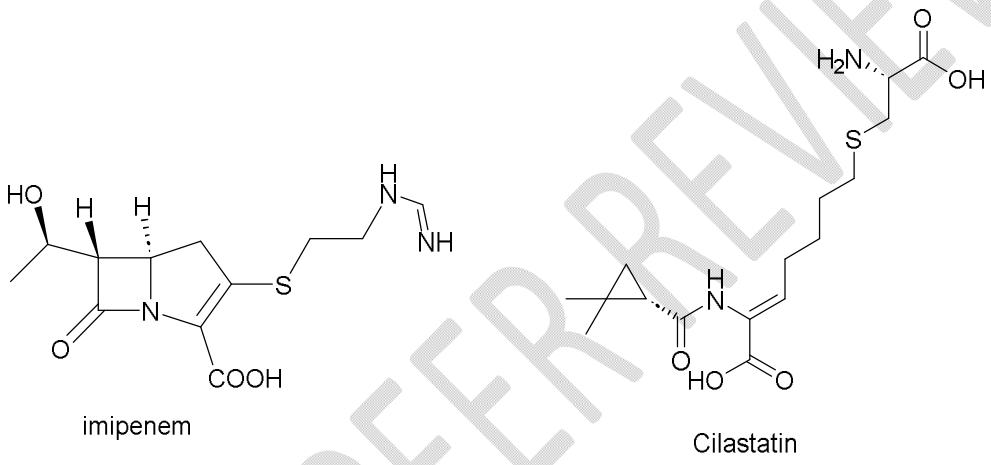


Figure 6: Chemical Structure of Imipenem-Cilastatin

- **Internalization of the terminal amine of cysteamine in a cycle**

The second strategy of pharmacomodulations of the cysteamine chain consisted in the internalization of the terminal amine of cysteamine in a cyclic type pyrrolidine. Such an approach leads to a less flexible cysteaming chain and a larger steric crowding than the cysteamine amine. All this results in a reduced overall reactivity compared to cysteamine and therefore a blockage of the dimerization phenomena observed with Thienamycin in a biological environment. Thus, cyclization of thienamycin cysteamine to N-substituted pyrrolidine by an iminoethyl group resulted in Panipenem (**Figure 7**) [23, 25, 37, 38].

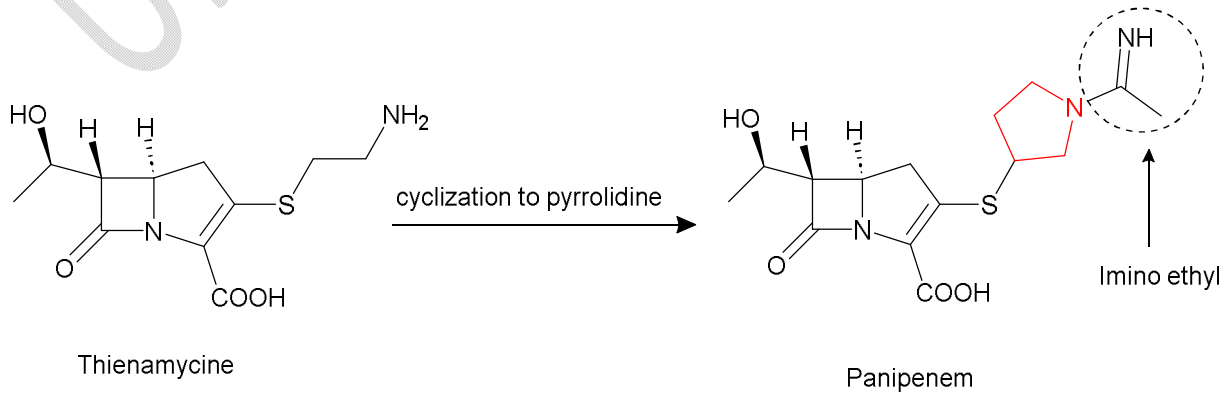


Figure 7: Cyclization of the terminal amine of cysteamine to pyrrolidine

Panipenem, which can be administered parenterally, has a broad spectrum of antibacterial action including aerobic or anaerobic Gram-positive and Gram-negative bacteria. It was introduced into therapeutics in 1993 in Japan for the treatment of surgical, gynecological, respiratory and urinary infections [39-42]. In addition, Panipenem is also susceptible to hydrolysis by the DHP-I enzyme such as Imipenem. To counteract this degradation, it is administered in combination with Betamipron, an inhibitor of tubular transport of organic anions (**Figure 8**). This combination, known as Carbenin®, has clinical and bacteriological efficacy comparable to that of Imipenem/Cilastatin in adults with respiratory or urinary tract infections. This combination has also been shown to be effective in treating surgical or gynecological infections in adults, as well as in children with respiratory and urinary tract infections in randomized clinical trials [43–45].

Panipenem/betamipron is well tolerated and few adverse reactions have been reported in clinical trials, most commonly elevated serum levels of hepatic transaminases, aspartate transaminase (AST) and alanine transaminase (ALT), eosinophils, rash, and diarrhea [46].

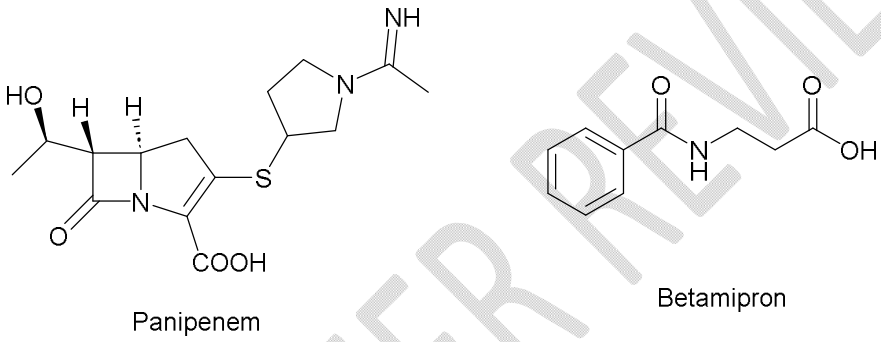


Figure 8: Chemical structure of Panipenem/Betamipron

2) Chemical modulation on carbon at position 4

To fight against hydrolysis of carbapenems by the DHP-I enzyme The pharmacomodulation strategy adopted consisted of introducing a methyl group into its configuration on the carbon at position 4. 4β-methylation increased the metabolic stability of the molecules by decreasing the susceptibility to hydrolysis by the βDHH-I, which contributes to the improvement of the therapeutic performance of carbapenems [47]. 4β-methylatedmolecules can beclassifiedintoderivatives:

- 4β-methylcarbapenems with pyrrolidine-like cyclic chain such as meropenem, ertapenem, doripenem, lenapenem and topolenem.
- 4β-methylcarbapenems with a non-pyrrolidine cyclic chain such as Biapenem and Tebipenem

2.1- 4β-methylpyrrolidine-like cyclic chain carbapenems

The molecules of this subgroup are characterized by the presence of 4β-methyl, which protects them against hydrolysis by DHH-I, allowing administration alone without the combination of DHP-I. In addition, the presence of a pyrrolidine-like cyclic chain contributes to better chemical stability and an absence of molecular dimerization. In addition, the nature of the substituents of the pyrrolidine chain influences the pharmacokinetic and therapeutic parameters of the molecules. Among these derivatives, the most prominent molecules are Meropenem, Ertapenem, Doripenem, Lenapeneme and Tomopenem [39, 41].

- **The Meropenem**

Meropenema is a 4β-methylcarbapenem with a thiopyrrolidine chain substituted by an amide-like function *N,N*-dimethylcarboxamide. The presence of this chain enhances activity against Gram-negative bacteria, including *Pseudomonas aeruginosa* and may also explain the good tolerability of meropenem (**Figure 9**) at the level of the central nervous system [48].

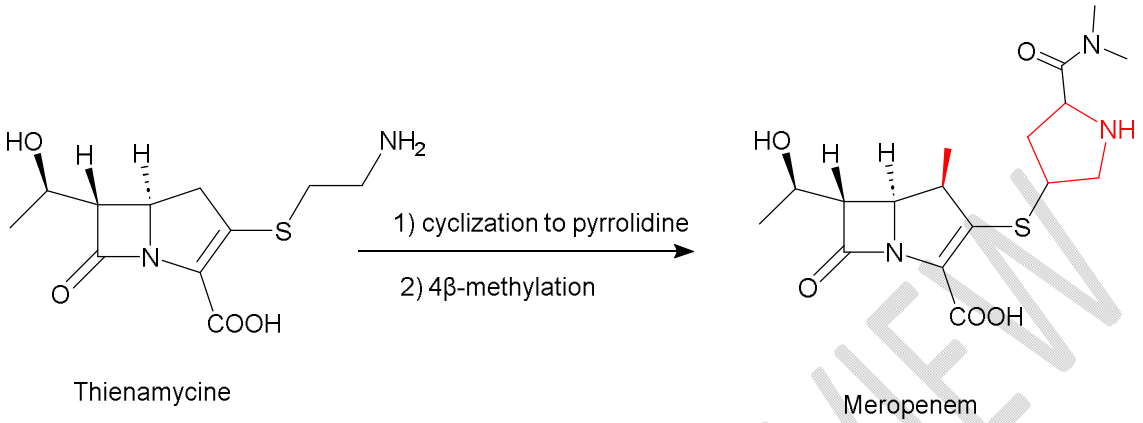


Figure 9: Chemical structure of Meropenem

- **The Doripenem**

Doripenem has many unique properties that place it at the top of the list as one of the most effective carbapenems. It exhibits better *in vitro* activityagainst*Pseudomonas aeruginosa* compared to other anti-pseudomonal carbapenems. It combines both the antibacterial spectrum of Imipenem against Gram-positive bacteria and that of Meropenem against Gram-negative bacteria. This particularity of Doripenem (**Figure 10**) is explained by the presence in its chemical structure of a thiopyrrolidine chain carrying a methylamino sulfamoyl group. This unique structure enhances its affinity for penicillin-binding proteins (PLPs) essential for bacterial wall synthesis. In addition, the molecule accumulates particularly in harsh environments (hypoxic environments, acidic environments) making it a particularly suitable choice for complex intra-abdominal infections, nosocomial pneumonia and complicated urinary tract infections. It also exhibits increased resistance to hydrolysis by renal dihydropeptidases due to β-methylation at position 4.

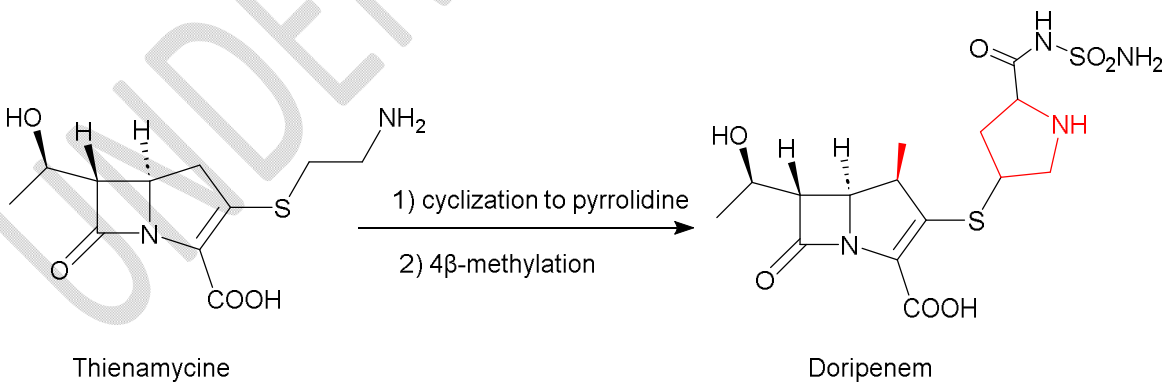
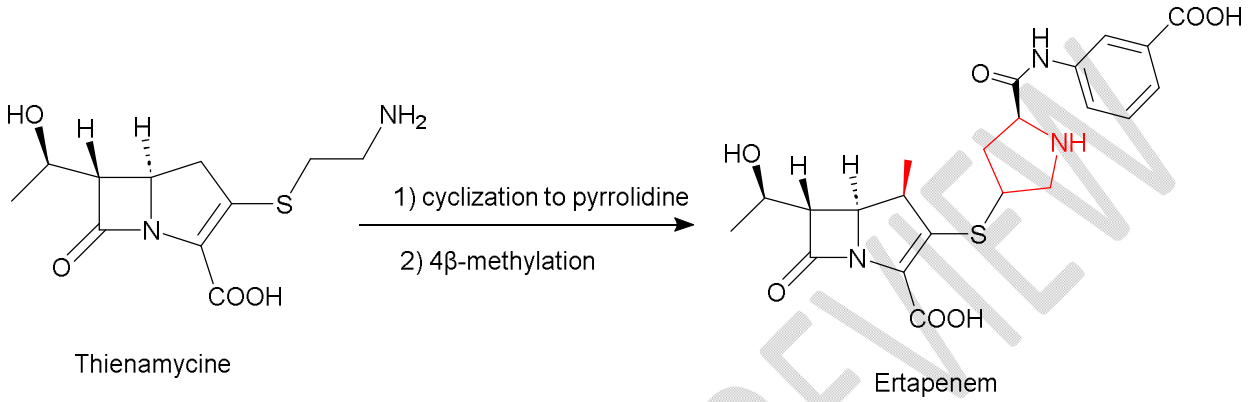


Figure 10: Chemical structure of Doripenem

- **The Ertapénem**

Ertapenem, developed in 2001, differs from Meropenem by the presence of a carboxyphenylcarbamoyl substituent on the thiopyrrolidine-like side chain. The presence of a substituent gives Ertapenem (**Figure 11**) a long half-life, allowing for once-daily administration. In addition, this chemical modification promotes strong

binding to plasma proteins, thereby reducing its clearance and contributing to a prolonged half-life time in the body. Unlike other carbapenems (Meropenem, Imipenem, Ertapenem), it has limited antibacterial activity against *Pseudomonas aeruginosa* and *Acinetobacter spp.*. However, this lower activity is compensated by excellent efficacy against other common pathogens, such as enterobacteriaceae, streptococci and anaerobes. In addition, the presence of β-methyl at position 4 makes the molecule less sensitive to hydrolysis by renal dehydropeptidase I. Ertapenem is also distinguished by a low potential for renal and neurological toxicity, enhancing its safety profile, particularly in elderly patients or patients with impaired renal function [49–54].

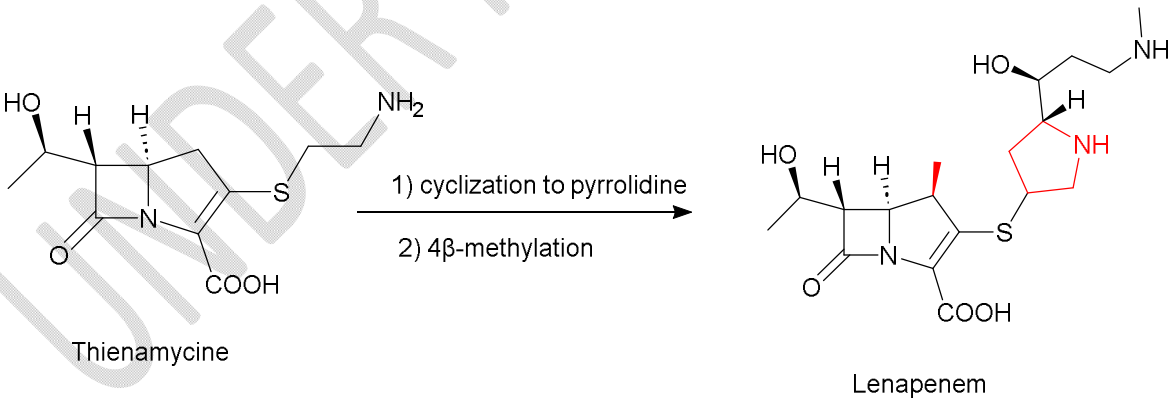


Thienamycine Ertapenem

Figure 11: Chemical structure of Ertapenem

- **Lenapene.**

Lenapenem is a molecule that differs from meropenem in the presence of a hydroxy aminopropyl on its thiopyrrolidine side chain. The presence of the hydroxy aminopropyl motif gives the molecule a Notable activity against *Pseudomonas aeruginosa*, including against Imipenem-resistant strains[56]. In addition, the activity of the molecule against Gram-positive cocci is higher than that of other carbapenems but lower than that of Imipenem. The Lenapenem (**Figure 12**) has shown therapeutic efficacy comparable to that of Imipenem/cilastatin in systemic infections due to Gram-positive and Gram-negative bacteria in mice [56–59]. However, its pharmacochemical development was halted in the 1990s due to several liver function abnormalities in phase II clinical trials [56–59] .



Thienamycine Lenapenem

Figure 12: Chemical structure of Lenapenem

- **Tomopenem**

Tomopenem (CS-023) is a 4β-methylcarbapenem with a broad antibacterial spectrum that covers both Gram-positive and Gram-negative bacteria. It is characterized by the presence of a thiopyrrolidine chain carrying a *N*-(1-acetylpyrrolidin-3-yl)-2-((diaminomethylene)amino)acetamide [60]. It shows moderate activity against *Staphylococcus aureus* methicillin-resistant (MRSA), with MIC90 between 4 and 8 mg/mL. It also induced antibacterial activity against the genus *Pseudomonas aeruginosa*, with inhibitory concentrations higher than those

of Meropenem. The development of Tomopenem (**Figure 13**) initially undertaken by Roche Laboratories under license from Sankyo, was discontinued in Phase II clinical studies [61, 62].

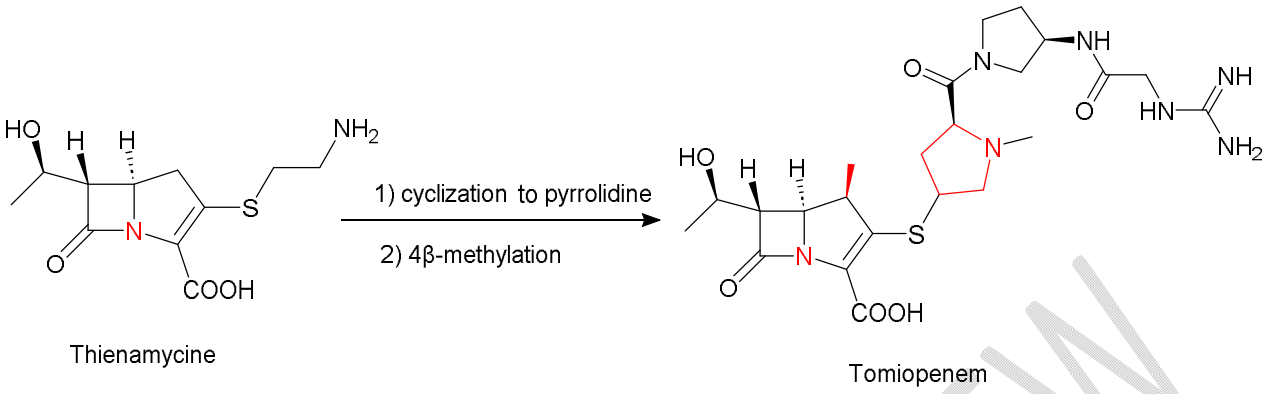


Figure 13: Chemical structure of Tomopenem

2.2- 4β-methylcarbapenems with non-pyrrolidine cyclic chain

- **Biapena**

Biapenem is an intravenous 4β-methylcarbapenem that has a broad spectrum of antibacterial activity, including Gram-positive, Gram-negative, aerobic and anaerobic bacteria. It has the particularity of having a thio pyrazolo-type side chain[1,2-*has*]triazole giving it a certain chemical stability [63]. The Biapenem (**Figure 14**) demonstrates clinical efficacy comparable to that of imipenem/cilastatin in the treatment of complicated intra-abdominal infections, lower respiratory infections and complicated urinary tract infections. It also showed good tissue penetration (lungs, abdominal cavity) and poor plasma protein binding (approximately 3.7%). Well tolerated, the most common side effects include rash, nausea and diarrhea [64]. In terms of activity, it is effective against β-lactamase-producing pathogens, but less so against carbapenem-resistant strains, such as some species of Pseudomonas aeruginosa. Biapenem, approved in 2002 in Japan, is recommended at a dose of 300 mg twice daily as a 30-60 minute infusion [63–65].

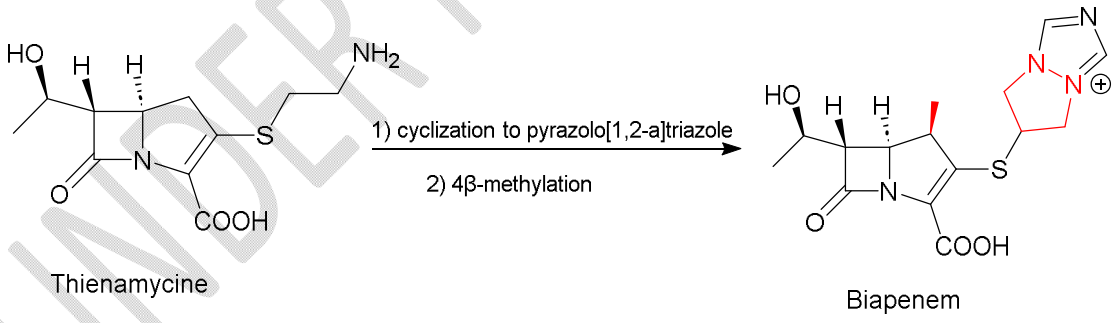


Figure 14: Chemical structure of Biapenem

IV-Oral Carbapenems

Oral carbapenems are a subgroup of carbapenems characterized by their ability to be administered orally. They share the antibacterial properties of intravenous carbapenems, with a broad spectrum of activity against Gram-positive, Gram-negative and some anaerobic bacteria. Their particularity lies in their oral bioavailability, achieved through structural modifications that stabilize the active compound and promote its absorption in the

gastrointestinal tract. In therapeutics, there are currently four molecules belonging to three chemical classes: penems, thiopenems and trinems.

Oral carbapenems have a major advantage in allowing patients to be treated effectively outside of the hospital setting. Unlike intravenous administration, which requires a sterile environment, specific skills and adapted infrastructure, oral forms offer simpler and more autonomous management. This method of administration thus avoids the constraints associated with the infusion, such as the impossibility for patients to self-administer, the risks associated with improper handling of the equipment or the practical inconvenience for the patient. In addition, it promotes a better quality of life for patients while reducing the burden on healthcare facilities.

IV.1-Oral active peneme derivatives

Tebipenem is the first oral 4β-methylcarbapenem developed by Wyeth Lederle Japan in 1994. It was developed for the treatment of otolaryngological and respiratory infections caused by *Streptococcus pneumoniae* Drug-resistant in pediatric patients [66].

Structurally, it differs from other carbapenems by the presence at position 3 of a side chain of the thioazetidinyl 1,3-thiazoline and non-pyrrolidine type. This chain gives the molecule a certain chemical stability in a gastric acid environment. In addition, its oral absorption is enhanced by the formulation of a prodrug Tebipenem-pivoxil at the level of carboxylic acid function. The latter showed a higher absorption than other existing β-lactam antibiotics in the form of a prodrug. Once absorbed, the prodrug is hydrolyzed to release the active molecule, Tebipenem (**Figure 15**). Tebipenem is approved in Japan for the treatment of susceptible germ infections in children, as it is more tolerable than infusion molecules [67–70].

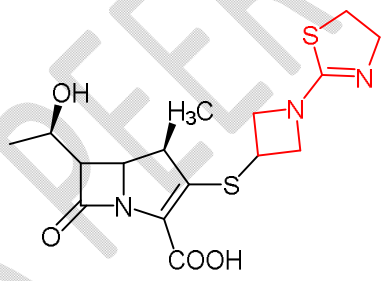


Figure 15: Chemical structure of Tebipenem

IV.2-Oral active thiopenem derivatives

Thiopenems are a subgroup of β-lactam ring antibiotics that are related to carbapenems, but characterized by the presence of a sulfur atom in their chemical structure. This sulfur is usually found in the ring adjacent to the β-lactam ring, which gives these compounds distinct chemical and pharmacological properties. The two representatives currently used in therapeutics are Faropenem and Sulopenem.

✓ **Sulopenem**

Sulopaenem, originally known under CP-70,429 (**Figure 16**) is an orally and parenterally active thiopenem derivative with a broad spectrum of activity against Gram-positive and Gram-negative bacteria. It has therapeutic potential for the treatment of urinary tract infections and intra-abdominal infections. However, Sulopenem is inactive against *Pseudomonas aeruginosa* and *Xanthomonas maltophilia*. [57, 71, 72]. In October 2024, the Food and Drug Administration (FDA) approved a combination of Sulopenem-Etzadroxil and probenecid, marketed as ORLYNVAH™, to treat UTIs caused by *Escherichia coli*, *Klebsiella pneumoniae* or *Proteus mirabilis* in women with limited oral treatment options [73].

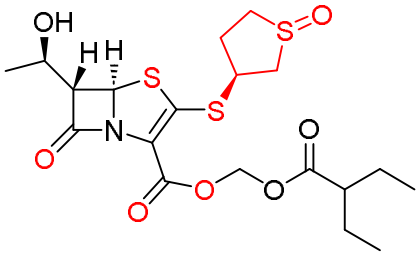


Figure 16: Chemical Structure of Sulopenem-Etzadroxil

Studies of structure-activity relationships (**Figure 17**) initiatives around the molecule have shown that it has retained the structural advantages of injectable carbapenems. In addition, the presence of a sulfur atom in the thiazolidine ring increases the high reactivity of the carbonyl of the β-lactam ring which causes an increase in antibacterial activities. The (S) orientation of the tetrahydrothiophene 1-oxide ring at position 3 imparts increased hydrolysis stability, better absorption, and high urinary concentration, which is essential for treating urinary tract infections. In addition, the presence of this neutral side chain increases the chemical stability of the molecule during formulation and reduces the effects on the central nervous system. In addition, esterification by etzadroxil (Ethyl 2-ethylbutyrate) improves its stability and oral bioavailability. Finally, sulfurprovidesresistance to degradation by DHP-1 [74].

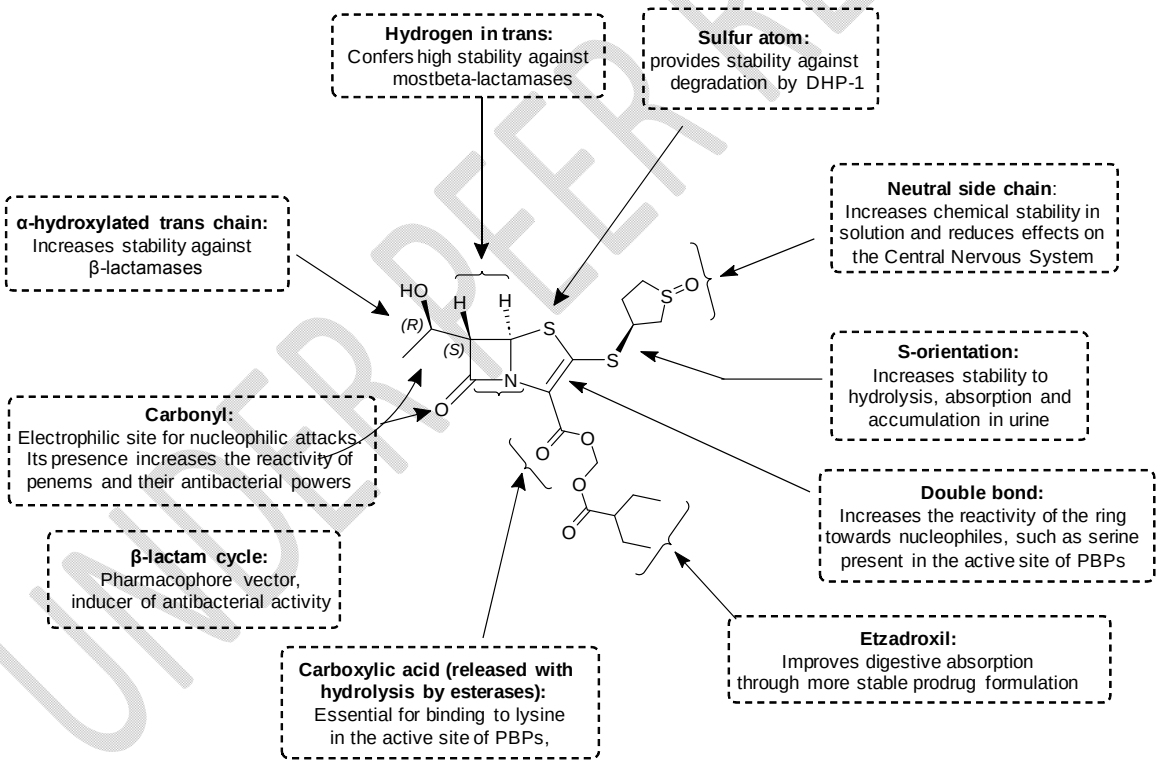


Figure 17: Diagram of structure-activity relationships around of Sulopénem[74]

✓ **My Faropene**

The Faropenem (**Figure 18**) is a structural analogue of Sulopenem chemically characterized by the present tetrahydrofuran chain position 3 which confers better chemical stability and reduced side effects on the central nervous system compared to Imipenem [75]. It exhibits a spectrum of antibacterial action against many aerobic and anaerobic Gram-positive and Gram-negative bacteria *in vitro*. It is particularly resistant to hydrolysis by almost all β-lactamases, including extended-spectrum β-lactamases (ESBLs) and AmpCβ-lactamases. However, it is

inactive against *Staphylococcus aureus* methicillin-resistant, *Enterococcus faecium* vancomycin resistant, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*[76]. Randomized, multicenter clinical trials of its esterified form Faropenem-medoxomil have shown that its efficacy and safety are equivalent to those of several common antibiotics (cefuroxime, clarithromycin, azithromycin, amoxicillin, cefpodoxime, and amoxicillin-clavulanic acid) in the treatment of various community-acquired infections [77]. However, the Food and Drug Administration (FDA) denied its approval, citing methodological limitations in clinical trials, including the lack of a placebo comparator for some indications and insufficient data for others [78].

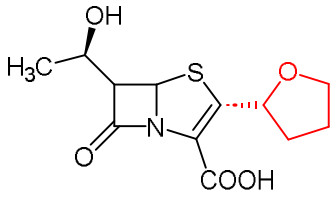


Figure 18 : Chemical structure of Faropenem

IV.3-Orally active trinem derivatives

Sanfetrinem is a tricyclic carbapenem or trineme. It is the first tricyclic molecule developed in the 1990s by Glaxo Wellcome[79]. Sanfetrinem possesses antibacterial activities against various Gram-positive bacteria, such as *S. aureus* and *S. pneumoniae*, as well as Gram-negative, in particular *E. coli* and *M. catarrhalis* [59, 80]. A Phase II clinical trial of Sanfetrinem-Cilexetil (**Figure 19**) was proven effective in treating respiratory infections in 1999. However, the development of SanfetrinemCilexetil that has been halted since that trial was restarted in 2022 in a new phase II clinical trial in the treatment of rifampicin-sensitive pulmonary tuberculosis [81]. The growing interest of Sanfetrinem in the fight against tuberculosis is justified by the fact that it has a broad spectrum of action against clinical isolates of *Mycobacterium tuberculosis*, including resistant strains. In addition, it has shown synergy of action with amoxicillin, ethambutol, rifampicin and rifapentine in a model of infection *in vivo*[82, 83].

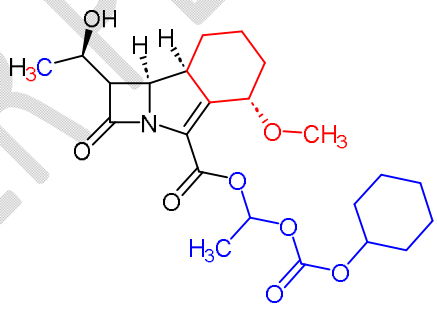


Figure 19: Chemical structure of Sanfetrinem-Cilexetil

V-Combinations of Carbapenems with β-Lactamase Inhibitors

The combination of carbapenems with β-lactamase inhibitors aims to fight infections due to multidrug-resistant bacteria, especially Gram-negative bacteria. These combinations aim to restore the effectiveness of carbapenems against resistance mechanisms such as extended-spectrum β-lactamases (ESBLs) or carbapenemases. Currently, the two combinations of carbapenems with β-lactamase inhibitors on the market are:

✓ **Imipénem-cilastatine-relebactam**

Relebactam is a potent beta-lactamase inhibitor with a diazabicyclooctane structure structural analogue of Avibactam. It differs from Avibactam in the presence of a piperidine on the acylaminated chain at position 2 of relebactam, which enhances its properties as a beta-lactamase inhibitor. In addition, the presence of the chemical

motif aminoxy sulfate with an electroattractor character gives relebactam a very high reactivity with respect to bases, nucleophiles and beta-lactamases. This high reactivity is responsible for a powerful inhibitory activity of beta-lactamases at pH 4 between 8. In addition, the protonation of piperidine at physiological pH prevents the efflux of relebactam out of bacterial cells, thus ensuring its effectiveness in the bacterial cell. The spectrum of inhibition of relebactam is mainly oriented towards class A carbapenemases (in particular KPC) and certain class D oxacillinases [84–86].

Relebactam in combination with imipenem-cilastatin (**Figure 20**) has been approved by the Food and Drug Administration (FDA) for the treatment of complicated bacterial infections of the urinary tract when no treatment options are available [87] This combination is also recommended to treat complicated intra-abdominal bacterial infections and nosocomial pneumonia associated with mechanical ventilation. It has good activity against KPC-producing strains and some multidrug-resistant bacteria, while offering better tolerance compared to polymyxins.

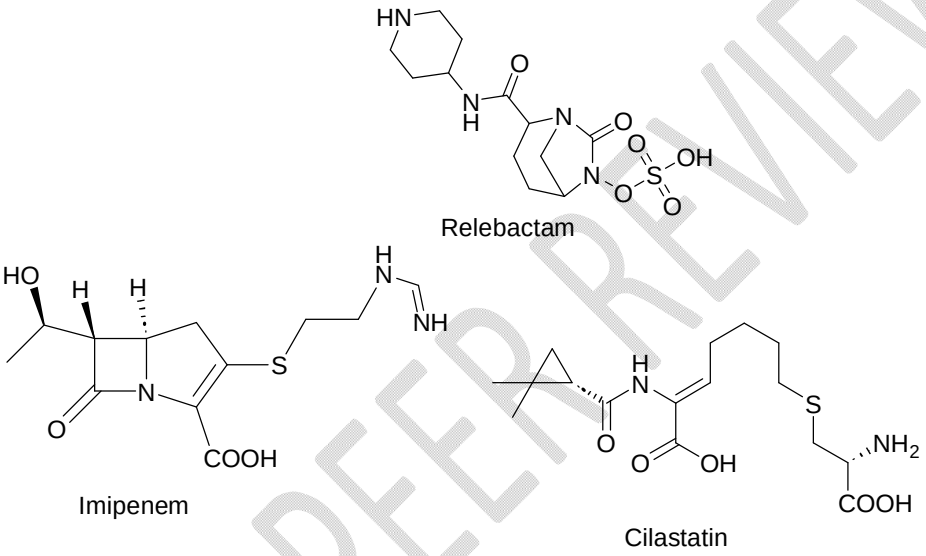


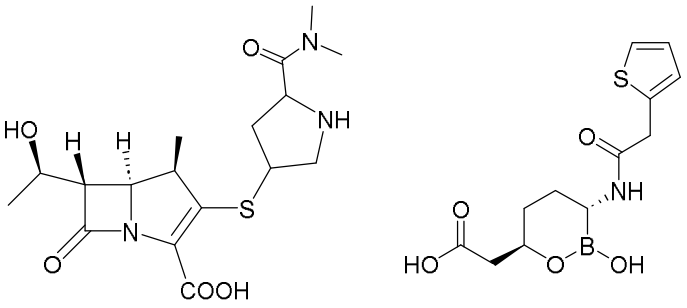
Figure 20 : Association imipénem-cilastatine-relebactam

✓ **Meropenem– vaborbactam**

Le meropénem-vaborbactam (**Figure 21**) is the second approved combination therapy of meropenem and vaborbactam[88]. Vaborbactam is a β-lactamase inhibitor derived from boronic acid. It has been designed to specifically counteract certain enzymes responsible for carbapenem resistance, including Class A carbapenemases, such as Klebsiella pneumoniae carbapenemases (KPCs), and certain Class C β-lactamases (AmpC). It remains ineffective against metallo-β-lactamase-producing bacteria (class B) and certain oxacillinases (class D). This combination restores the effectiveness of meropenem against resistant strains. In addition, the combination showed favorable pharmacokinetic properties, with mainly renal elimination and good tissue penetration, including in the lungs [89, 90].

The TANGO I and II trials showed that the efficacy of this combination was superior to or comparable to that of standard treatments (polymyxin, tigecycline), with a better safety profile and a low risk of nephrotoxicity. The combination is particularly effective as monotherapy to treat infections induced by Klebsiella pneumoniae carbapenemase (KPC)-producing bacteria, even in the presence of certain ceftazidime-avibactam-resistant KPC mutations [91, 92]

Meropenem-vaborbactam is approved for the treatment of serious infections, including complicated urinary tract infections, intra-abdominal infections, nosocomial pneumonias, and sepsis caused by multidrug-resistant Enterobacteriaceae [93].



Meropenem Vaborbactam

Figure 21: Meropenem–vaborbactam combination

Although promising, these combinations require rational use to avoid the emergence of new resistances. In addition, new combinations with other inhibitors must be considered to extend the spectrum of antibacterial action to metallo-β-lactamase-producing bacteria (class B).

Conclusion

The interest of our study lies in understanding the pharmacochemical evolution of Thienamycin to hemisynthetic carbapenems, in order to guide future pharmacomodulations that may lead to more effective compounds better adapted to the current challenges of fighting bacterial infections. As a result of our analysis, several important conclusions can be drawn regarding structure-activity relationships in the carbapenem class.

Thienamycin's unique structure, including its β-lactam nucleus fused to a pyrrolidine ring, forms the basis for its broad spectrum of antibacterial activity. However, its chemical instability, due in particular to the reactivity of the primary amine function of cysteamine, required structural modifications. Hemisynthetic carbapenems such as Imipenem and Meropenem have undergone several chemical modulations that have improved their chemical stability, bioavailability and clinical efficacy. The introduction of specific substituents at the C2 and C4 positions has been shown to modulate both chemical stability, oral administration and the spectrum of antibacterial activity. In addition, the combination with specific carbapenemase inhibitors, such as Relebactam or Avibactam, represents a promising strategy to overcome emerging resistance mechanisms.

Despite these advances, challenges remain. The increased resistance to carbapenems, in particular through the production of carbapenemases such as KPC, NDM or OXA, highlights the need to develop new derivatives capable of circumventing these mechanisms.

Thus, after several decades of clinical use, carbapenems continue to play a central role in anti-infection therapeutics. The nextgenerations of carbapenems are expectedto:

- Be active against carbapenemase-producing bacteria such as KPC, NDM and OXA;
- Improve their affinity for Gram-negative bacteria while maintaining their efficacy on Gram-positive bacteria;
- Improvetheir oral activity
- Reducing side effects on the central nervous system after their administration.

The study of the pharmacochemical evolution of carbapenems provides essential clarification on the structural elements essential for the maintenance of their antibacterial activity. This information paves the way for targeted pharmacomodulations to address unmet medical needs. Among the areas for improvement, wecouldconsider:

- Chemical stabilization via bioisosteric groups at the C2 position;
- The integration of hydrophilic substituents for better activity on Gram-negative bacteria;
- The development of new inhibitors targeting the most versatile carbapenemases.

These efforts will ensure the sustainability of carbapenems in the face of the constant evolution of bacterial resistance, thus guaranteeing their place on the front line in the fight against severe and multi-resistant infections.

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