

REVIEW ARTICLE

Cephems: Fifty Years of Continuous Research

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Since 1964, seven waves of parenteral cepheims have been reported. All of them were designed to meet medical needs. The first (group I) and the third (group III) waves were very successful and drugs belonging to group III are widely used in the treatment of severe infections. A new series of compounds (group VII), with a new compound under development was designed for the treatment of *Staphylococcus aureus* strain resistant to methicillin but also to glyco- and lipoglycopeptides. By modifying the substituent at position 3 and 7 of the cepheims rings optimal moieties have been fixed leading to potent anti-Gram-positive drugs.

Alterations of substituents are still in progress to obtain optimal anti-Gram-positive (anti-MRSA) compounds.

The first oral cephem cephalixin was introduced in clinical practice in 1967. Since this time, many esterified and non-esterified cepheims have been synthesized and introduced in clinics. There are two groups of compounds, α -amino and non- α -amino cepheims which are classified in six groups according to their chemical structure. The absorption route was explored, and three transporting systems have been described according to the physico-chemical properties of these compounds, in addition prodrugs are passively absorbed.

Sulphonamides, thyrothrycin and penicillin G were the forerunner for an intensive successful research for discoveries of new antibacterial agents. Many teams were looking after new compounds, especially possessing a broad antibacterial spectrum.

The success of penicillin G had an unexpected effect on increasing number of *Staphylococcus aureus* isolates resistant to penicillin G in London hospitals and these strains spread progressively all around the world. Research of novel antibacterial agents was extremely important. Many compounds issued from fermentation broth of *Streptomyces* having antibacterial activity were screened against *S. aureus* isolates resistant to penicillin G such as erythromycin and vancomycin. Semi-synthetic penicillins such as methicillin, oxacillin and derivatives exhibiting antistaphylococcal activity against *S. aureus* isolates producing penicillinases were synthesized in 1950s.

In Sardinia, in 1945 G. BROTZU discovered that

fermentation products extracted from *Cephalosporium acremonium* (*Acremonium chryseogenum*) exhibited anti-Gram-positive and -negative activities. *C. acremonium* were isolated from the sea near a sewage outfall at Cagliari, Sardinia. The fermentation extracts were administered locally for the treatment of wound infections successfully¹⁾. BROTZU was unable to purify the *C. acremonium* extracts. He contacted Oxford chemical team who was successful with penicillin to extract and purify the components of this fermentation.

NEWTON and ABRAHAM in 1953, discovered cephalosporin C²⁾. Cephalosporin C was found to have several remarkable properties, being active against *E. coli*, *S. typhi*, and the Oxford strain of *S. aureus*, but also resistant to penicillinase hydrolysis from *Bacillus subtilis*. The chemical structure was elucidated in 1959³⁾. In 1960, small amounts of 7-amino-cephalosporinic acid (7-ACA) were obtained by acid hydrolysis of cephalosporin C.

A chemical procedure by which the α -aminoadipyl side-chain could be removed to produce 7-ACA in good yield was developed in 1962.^{3a)} Four classifications have been described: biological⁴⁾, microbiological⁵⁾, chemical^{6,7)} and pharmacokinetics⁵⁾.

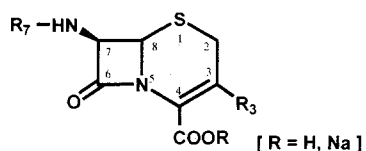
Chemical classification is supported either by ring alterations or by substituent alterations.

1. Parenteral Cephalosporins

Seven waves of parenteral cephalosporins support the microbiological classification in which cephems are divided in seven groups according to the antibacterial spectrum. The development of numerous compounds, which were introduced in clinical practice, allowed to divide cephems in three pharmacokinetic groups according to their apparent elimination half-life.

In 1964, cephalothin and cephaloridine were introduced in clinical practice and were followed by cefazolin. Cephaloridin was the first cephems with a C-3 azolium heterocycle substituent. Many compounds were synthesized and composed group I of the microbiological classification.

Parenteral Cephem: Group I



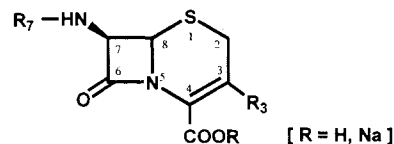
	R ₃	R ₇
Cephalothin	-CH ₂ OCOCH ₃	
Cephaloridine	-CH ₂ -N ⁺ (C ₆ H ₅)	
Cefazolin		

These analogues were prepared to overcome *S. aureus* resistance to penicillin G. The second aim was to prepare compounds with new C-3 side chain to avoid metabolism and to length the apparent elimination half-life. One compound, cefazolin possesses a long apparent half-life.

The successful introduction of ampicillin in clinical practice, which exhibits anti-Gram-negative activity, was rapidly followed by emergence of clinical isolates resistant to ampicillin by production of broad spectrum β -lactamases.

Research for new cephem derivatives was designed for overcoming β -lactamase production in Gram-negative bacteria and these compounds belong to group II.

Parenteral Cephem: Group II



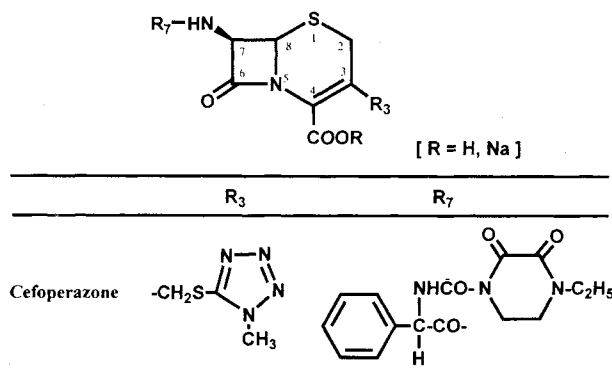
	R ₃	R ₇
Cefuroxime	-CH ₂ OCONH ₂	
Cefamandole		
Cefonicid		

At the beginning of the 1970s reports appeared that certain species of *Streptomyces* produced 7- α -methoxy cephalosporins⁵⁾. These molecules were named cephamycins. The presence of an 7- α -methoxy group in the cephem ring was found to be associated higher resistance to hydrolysis by most β -lactamases. During the 1970s several new cephalosporins with useful activity against Gram-negative bacilli were prepared by further alterations of the C-3 and C-7 side chains.

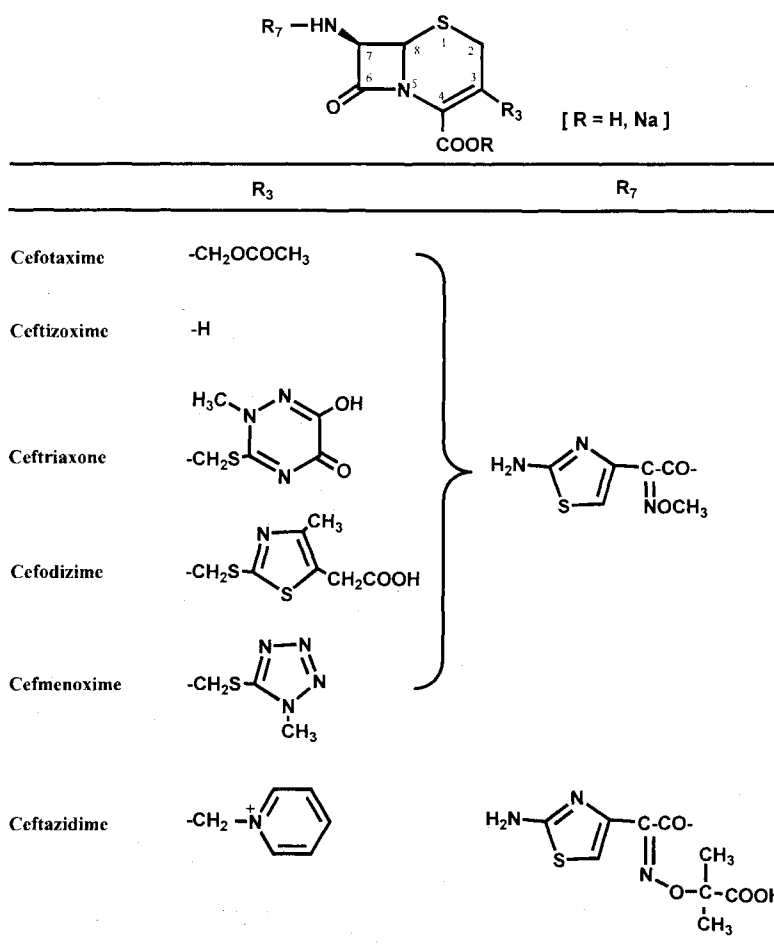
Two important discoveries in the field of cephems were reported: the *syn* methoxyimino residue at C-7 position of the cephem ring with cefuroxime and the methyltetrazolthio ring which results in enhancement of *in vitro* activity with cefamandole. These compounds of group II were introduced in clinical practice in 1979~1980. In general these cephems are less active than group I compounds against staphylococci and streptococci but are more active against selected Gram-negative bacilli. All cephems possess an apparent elimination half-life range from 1 to 3 hours. One compound with a modification on the C-3 tetrazolyl ring, having a sulfonic group instead a methyl group on the C-3 tetrazolyl ring, cefonicid, possesses a long apparent elimination half-life of 5 hours⁵⁾.

A continuous flux of new compounds issued from chemical alterations conducted to design new derivatives to overcome β -lactamases hydrolysis, allowed the first compounds of group III to be developed, cefotaxime^{8,9)}.

Parenteral Cephem: Group IIIA



Parenteral Cephem: Group IIIB



In parallel, two types of compounds have been synthesized, *N*-acyl cephalosporins represented by cefoperazone, or 2-amino-5-thiazolyl cephalosporins represented by cefotaxime, all of them are included in group III. A given cephem could be inserted in group III, if it possesses at least two of the following characteristics: the chemical structure may have a 2-amino-5-thiazolyl ring, stability to broad spectrum β -lactamase hydrolysis, good activity against Gram-negative bacilli, e.g.

Enterobacteriaceae, or fastidious Gram-negative bacilli, or antipseudomonal activity.

Cefotaxime was the first 2-amino-5-thiazolyl cephem having a *syn* methoxyimino residue at C-7. The C-3 chain is an acetoxymethyl moiety. The *syn*-methoxyimino group is responsible for the high stability to β -lactamase hydrolysis by broad-spectrum β -lactamase.

The introduction of the 2-amino-5-thiazolyl ring in the C-7 side chain is a major advance in cephalosporin research.

Table 1. Cephems activities against *S. pneumoniae* with different patterns of resistance to penicillin G¹³⁾.

	Peni-S (MIC < 0.12 mg/l)		Peni-I (MIC 0.12 ≤ 1.0 mg/l)		Peni-R (MIC > 1.0 mg/l)	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Cefotaxime	0.03	0.03	0.25	1.0	1.0	2.0
Ceftriaxone	0.03	0.03	0.25	1.0	1.0	2.0
Ceftazidime	0.25	0.25	2.0	16.0	16.0	16.0
Ceftizoxime	0.06	0.06	0.5	8.0	16.0	16.0
Cefodizime	0.03	0.03	0.5	2.0	2.0	4.0
Cefpirome	0.01	0.03	0.12	0.5	0.5	1.0
Cefepime	0.03	0.12	0.12	0.5	1.0	1.0

This ring is responsible for the breakthrough in antibacterial activity. It is more than 100 times more potent than cefamandole.

Numerous other 2-amino-5-thiazolyl cepheems were synthesized and introduced in clinical practice. They have other substituents at position 3 of the cephem ring than cefotaxime. At least, five compounds in addition of cefotaxime were introduced in clinical practice: ceftizoxime, ceftriaxone, cefodizime, ceftazidime and cefmenoxime.

The C-7 substituent is responsible for pharmacokinetic properties, like highlighted with ceftriaxone, which possesses a triazine substituted ring, or cefodizime, which has a 3',5'-disubstituted thiazolyl ring¹⁰⁾. This substituent fixes on cefodizime is also responsible of non antibacterial activity such as immune properties¹¹⁾. The C-3 moiety is also responsible of antibacterial activity. This fact is highlighted by the inoculum size effect¹²⁾ or by differential activity against *S. pneumoniae* isolates resistant to penicillin G. Against these strains, only cefotaxime, ceftriaxone, cefpirome and cefepime exhibit good and therapeutical activity against *S. pneumoniae* multidrug resistant isolates (Table 1).

Ceftizoxime, ceftazidime, cefodizime are devoid of antibacterial activity against penicillin G resistant isolates¹³⁾.

A third line of compounds was obtained by introduction of an oxygen atom in the cephem ring instead of sulfur atom¹⁴⁾.

The first derivative introduced in clinical practice was latamoxef¹⁴⁾. Latamoxef is active against Enterobacteriaceae harboring broad spectrum β -lactamases and even extended spectrum β -lactamases. However, latamoxef is poorly or inactive against Gram-positive cocci. Latamoxef

was given up due to unexpected adverse events. The presence of an *N*-methyltetrazolthio ring at C-3' has been shown to be responsible for hypoprothrombinaemia (inhibition of vitamin K-epoxide reductase) and antabuse-like effect (inhibition of aldehyde dehydrogenase). The carboxylic group (C-7 side chain) can cause platelet dysfunction¹⁵⁾.

The C-3'-*N*-hydroxymethyltetrazolylthiomethyl group of flomoxef does not inhibit the aldehyde dehydrogenase¹⁶⁾ and is less inhibiting toward vitamin K-epoxide reductase than the *N*-methyl derivative. Flomoxef is less active than latamoxef against Enterobacteriaceae producing class C β -lactamases but shows a good *in vitro* activity against Gram-positive cocci. Other oxa-1-cepheems have been synthesized but none of them reached the development stage⁵⁾.

Today, three cephalosporins of group III remain major antibacterial drugs for treatment of severe infections: cefotaxime, ceftriaxone, and ceftazidime. A renewal of ceftizoxime is expected in Japan as an oral aminoacid prodrug, but due to the lack of activity against *S. pneumoniae* isolates resistant to penicillin G, this compound will have restricted clinical indication in respiratory tract infections.

Bacteria are very flexible and always found a way to escape the antibacterial activity. Group III compounds have weaknesses, they are devoid of activity against isolates producing class C β -lactamases (*e.g.* *Citrobacter freundii*, *M. morgani*, *S. marcescens*, *Enterobacter* spp.) and are hydrolyzed by so-called extended broad spectrum β -lactamases (ESBL) such as TEM-3 and followed, SHV-2 and followed, which hydrolyzed at various degrees cefotaxime and ceftazidime. ESBL enzymes are encountered mainly in *K. pneumoniae* but also in other Enterobacteriaceae species. The third weak point except for

ceftazidime is the poor antipseudomonal activity.

Researches were never stopped after the introduction in clinical practice of components of group III. The target was to enhance antipseudomonal, antistaphylococcal activities and to overcome class C β -lactamases.

Cefsulodin¹⁷⁾ and ceftazidime were the first cephalosporin with improved activity against *P. aeruginosa* to be used in clinical setting. They bear a 1-pyridinium group at the C-3 position. These two compounds are dianionic compounds¹⁸⁾. In the meantime, it was decided to stop to insert at C-3 position the *N*-methyltetrazolylthio ring due to unacceptable side effects. Group IV, containing C-3' quaternary ammonium cephem^{19,20)}, was issued from this research. These azolium derivatives are zwitterionic compounds. In group IV, other chemical alterations have been done, in order to increase antipseudomonal activity. Introduction of 5-amino-2-thiadiazolyl ring instead of 2-amino-5-thiazolyl ring allows enhancing the antipseudomonal activity but lead to a decrease of activity against Enterobacteriaceae (*i.e.* cefclidid, ceftuprenam)²¹⁾. Cefpirome, cefepime, cefclidid and ceftuprenam were introduced in clinical practice.

Due to their zwitterionic nature these compounds could enter through additional porin channels and rapidly reach their PBPs targets by exhibiting poor affinity for C class

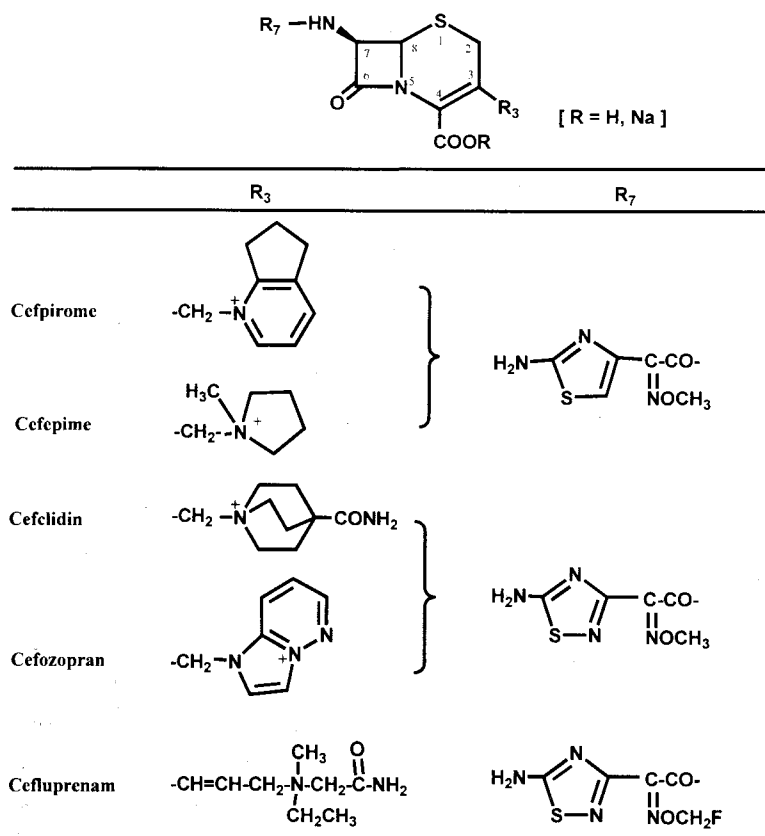
β -lactamases, which are located in periplasmic space. However, these compounds are hydrolyzed by ESBL and none of them show an elimination half-life above 3 hours in healthy volunteers.

In order to increase anti Gram-positive activities, different chemical modifications have been proposed. To add a C-3 vinyl moiety or to introduce an hydroxyimino chain instead of a methoxyimino residue at C-7 of the cephem ring⁵⁾. These compounds showed a significant enhancement of antistaphylococcal activity. Introduction of a monofluoromethoxyimino group at the 7-position led to a two-fold increase in activity against most bacteria as compared with the methoxyimino counterpart (ceftuprenam)⁵⁾.

The antipseudomonal activity is never satisfactory, quickly *P. aeruginosa* overcome the antibacterial activity of new compounds. Cephems which belong to group IV possess two or more of the following characteristics: the presence of a C-3' quaternary ammonium side chain and are zwitterionic compounds, a broad antibacterial spectrum including *P. aeruginosa*; good antibacterial activity against Enterobacteriaceae isolates producing class C enzymes. They have to fulfil the definition of group III⁵⁾.

All the C-3' quaternary ammonium compounds introduced for clinical use or under development possess

Parenteral Cephem: Group IV



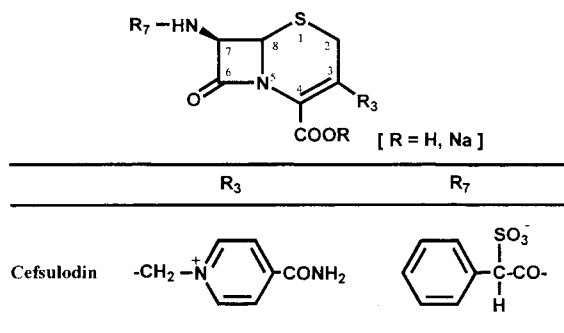
the same antibacterial activity as cefotaxime, but they differ by adding antipseudomonal activity²²). Due to the C-3' side chain, there are differences among these compounds. Against *S. pneumoniae*, the most active compound is cefpirome irrespective of the resistance phenotype to penicillin G. Against penicillin G resistant *S. pneumoniae* cefepime and ceftazidime exhibit comparable activity to cefotaxime. Ceftuprenam is weakly active and ceftidion is inactive²⁰).

New cepems were needed against Enterobacteriaceae producing ESBL and *P. aeruginosa*. New sets of cephalosporins, which composed group V, are catechol or pyridone-containing cepems. These catechol or pyridone moieties are fixed on the oxime residue. They act with a bifunctional mechanism of action, PBPs inhibition and iron chelation. None of them reached the registration stage. The most developed compound was cefticol²³). Some derivatives, such as RU59863 exhibited good antipseudomonal activity, and were able to overcome ESBL production and displayed good antistaphylococcal activity^{24,25}).

Research in catechol-containing cepems were given up due to the difficult chemistry, high cost of production, and risks of adverse events as it was shown with cefticol.

Today researches in the cepem field are more focused on narrow antibacterial spectrum antibacterial. The first narrow antibacterial spectrum cephalosporin, cefsulodin (group VI) was introduced in clinical practice in early 1980s. A renewal of interest on narrow antibacterial spectrum cepems arose against methicillin-resistant *S. aureus*²⁶). Many compounds have been investigated for

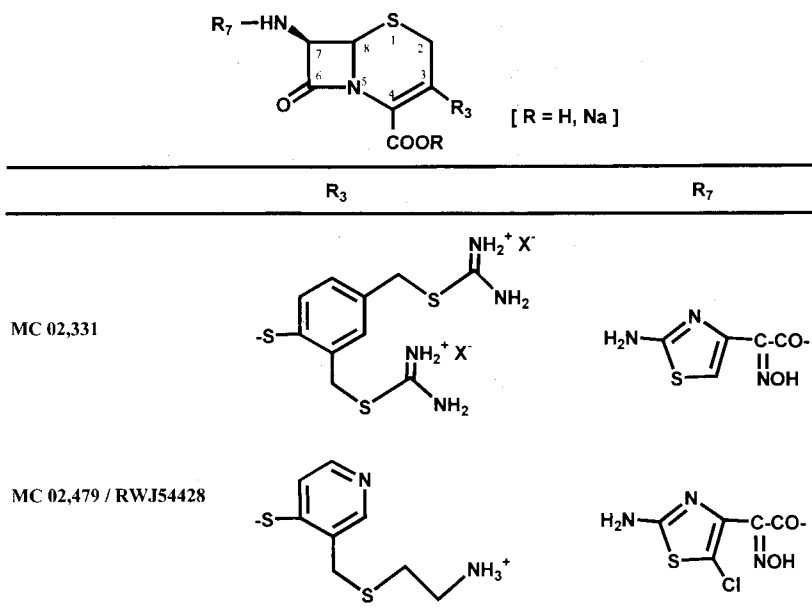
Parenteral Cepem: Group VI



anti-MRSA activities, within known family such as glycopeptide, or new chemical entities for human uses, such as oxazolidinones, evernimycin or new screened compounds.

By chemical alterations of the C-7 and C-3 substituents of the cepem ring, novel entities has been synthesized within carbacepems²⁷) or cephalosporins. The same type of research was ongoing in the carbapenem family^{28,29}). This group VII is composed of narrow spectrum cepems. One compound is currently underdevelopment RWJ 54428. The difficult task is to produce cepems, which provide activity against MRSA and against GISA strains. RWJ 54428³⁰) seems to be active against both methicillin and vancomycin *S. aureus* resistant (GISA) strains. One weakness knows for this compound is the poor water solubility. Prodrug derivatives has been prepared with improve solubility³¹).

Parenteral Cepem: Group VII



2. Oral Cephems

In parallel, but to a lesser extent, of the development of parenteral cephem, oral cephalosporins were semi-synthesized.

Cephalosporins are acid stable but poorly absorbed. Modifications of the side chain at the C-7 position of the cephem ring by fixing an D-phenylglycine moiety have given cephalixin in 1967³²). Since 1967 many series of compounds bearing a 7-D-phenylglycine residue were synthesized, but only few of them were introduced into clinical practice.

The aim of modifying the α -aminocephalosporins was to improve the pharmacokinetic profile by enhancing oral absorption. This goal was reached with cefadroxil, which differs from cephalixin by having an *p*-hydroxyphenyl moiety instead of a phenyl, allowing one to two oral administrations per day. Some esters were also prepared, such as cephaloglycin or cephalixin esters.

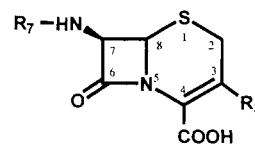
The second target was to enhance the antibacterial activity. The first group of oral cephem was directed against penicillinase-producing strains of *S. aureus*. The second series of oral cephem was oriented against Gram-negative bacilli. Polar group were appended at the C-3 position (cefactor, cefroxadine). In the development of parenteral cephem of group III, much effort was directed towards obtaining absorbable compounds. With cefotaxime and ceftriaxone, efforts were unsuccessful. Some success was realized with ceftizoxime (aminoacid prodrug of ceftizoxime). Two compounds were esterified and are widely used, cefuroxime-axetil and cefotiam-hexetil.

Within 2-amino-5-thiazolyl cephem, two types of compounds were developed, esterified and non-esterified. Non esterified cephem possess an hydroxy (cefdinir) or an acetoxy (cefixime) residue on the oxime group. Other groups have been added instead of the oxime group (ceftibuten). However, many of the new oral cephem are prodrugs with a cleavable ester at C-4 (carboxylic group). They differ in their C-3 side chain and ester chain. The main compounds are cefpodoxime-proxetil, cefetamet-pivoxil, cefcapene-pivoxil and cefditoren-pivoxil.

On the basis of chemical structure, oral cephem can be divided into seven groups.

Group I and II contain α -amino cephem. Group I contains most of the common old cephalosporins, which are divided into three subgroups according to their C-3 side chain. The subgroup Ia contains compounds with a C-3

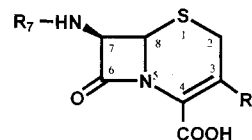
Oral Cephem: Group Ia



	R ₃	R ₇
Cefadroxil	-CH ₃	
Cephalixin	-CH ₃	
Cephradine	-CH ₃	
Cefprozil	-CH=CH-CH ₃	

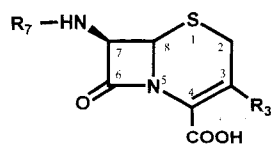
aliphatic side chain (cefadroxil, cephalixin, cefprozil, cephradine); the compounds of subgroup Ib possess a polar moiety at C-3 (cefactor, cefroxadine) and one compound belongs to group Ic having a C-3 aromatic ring (cefatrizine). Group II is for bicyclic α -amino derivatives,

Oral Cephem: Group Ib and Ic



	R ₃	R ₇
Cefactor	-Cl	
Cefroxadine	-OCH ₃	
Cefatrizine		

Oral Cephem: Group III and V



	R ₃	R ₇
Cefixime	-CH=CH ₂	
Cefdinir	-CH=CH ₂	
Ceftibuten	-H	

none of them reach the development stage. Group III is a group for miscellaneous cepheps (ceftibuten), group V for aryloxyimino derivatives (cefixime, cefdinir) and group VI contains carbacepems (loracarbef). Group IV is the more complex group, containing various types of cepheps with ester chain fixes on the C-4 carboxylic group.

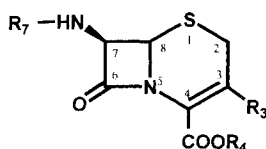
Group IV could be divided into four subgroups.

Subgroup IVa contains α -aminocephems, subgroup IVb is composed of non α -substituted cepheps (e.g. cefotiam-hexetil), subgroup IVc having the α -substituted cephalosporins, and subgroup IVd gathering aryloxyimino cephalosporins (cefuroxime-axetil, cefpodoxime-proxetil, cefetamet-pivoxil, cefcapene-pivoxil, cefditoren-pivoxil)³³.

Cepheps that exist as zwitterions (α -aminocephems), or anions (cefixime, ceftibuten) are uptake by di- or tripeptides transport system through the enteric membrane.

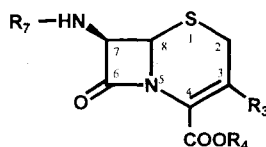
Transport of ceftibuten and cephalixin is stereospecific

Oral Cephem: Group IVb



	R ₃	R ₄	R ₇
Cefotiam hexetil			

Oral Cephem: Group IVd



	R ₃	R ₄	R ₇
Cefuroxime axetil	-CH ₂ OCONH ₂		
Cefpodoxime proxetil	-CH ₂ OCH ₃		
Cefetamet pivoxil	-CH ₃		
Cefditoren pivoxil			
Cefcapene pivoxil	-CH ₂ OCONH ₂		

depending on the isomerism of the side chain at the 7-position. The *cis*-isomer of ceftibuten and D-cephalexin are absorbed.

However, the cepheims transport is more complex. Three different carriers have been proposed: the first transport system carries hydrophobic compounds (α -amino cepheims); the second carrier is the concentrative transport system relatively hydrophilic (ceftibuten). The third carrier is a transport system for peptide with a heterocyclic aminoacid at the *N*-terminus (e.g. S-1090, an investigational oral cephem).

The C-4 ester increases the lipophilicity of the molecules, which diffuses passively through the intestinal mucosa.

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