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Design, Development and Synthesis of Novel Cephalosporin Group of Antibiotics

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1. Introduction

Cephalosporins are β- lactam antibiotics. In cephalosporin C, four membered β- lactam ring (which is mainly responsible for the activity) is fused with six membered dihydrothiazine ring to form the basic nucleus, 7-aminocephalosporanic acid (7-ACA) and to which α-aminoadipic acid side chain is attached through an amide bond (Fig 1). (Mandell and Sande,1991)Although cephalosporin was found to be active against large number of pathogenic bacteria (Medeiros, 1997) but the main hindrance in its application is its low stability. Also, occurrence of bacterial strains that are resistant to already existing antibiotics such as methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *E. faecalis* (VRE) has led to the search of new semisynthetic cephalosporins with better solubility and new mechanism of action. Only cephalosporin C is found naturally, so it's chemical modification allowed production of a whole series of semisynthetic cephalosporins which can be used as therapeutics to fight organisms that have become penicillin resistant. Chemical modifications of cephalosporin C resulted in new cephalosporin derivatives. These semisynthetic cephalosporins are classified based on their activity profile, the antibacterial spectrum. Each newer generation of cephalosporin has significantly greater Gram –ve antimicrobial properties than the preceding generations, (Stan,2004; Jones,1994; Jacoby,2000; Babini and Livermore, 2000) in most cases with decreased activity against Gram +ve organism. Fourth generation cephalosporins are known to have true broad spectrum activity. (Wilson,1998; Tzouvelekis et al., 1998) In the past decade, even though the cephalosporin antibiotics have made remarkable progress and contribution in the treatment of acute diseases originated from pathogenic infection in clinics, many efforts still exist to achieve the well balanced broad spectrum and to improve beta-lactamase stability. 7α-formamido cephalosporins were isolated as fermentation product of various gram negative bacteria. The development of a new antibiotic focuses mainly with the study and characterization of its mechanism of its activity (Table 1). The β-lactam antibiotics like penicillin, cephalosporins, vancomycin, etc. are specific inhibitor working against bacterial cell wall (peptidoglycan) synthesis but newer strains have β-lactamase activity which destroys most of the β-lactam antibiotics and thus make them resistant to it. However, cephalosporins proved to be more stable to β-lactamase. Cephalosporin-C (CPC) shows similarity to in structure with the penicillin in having an acyl side chain attached to an

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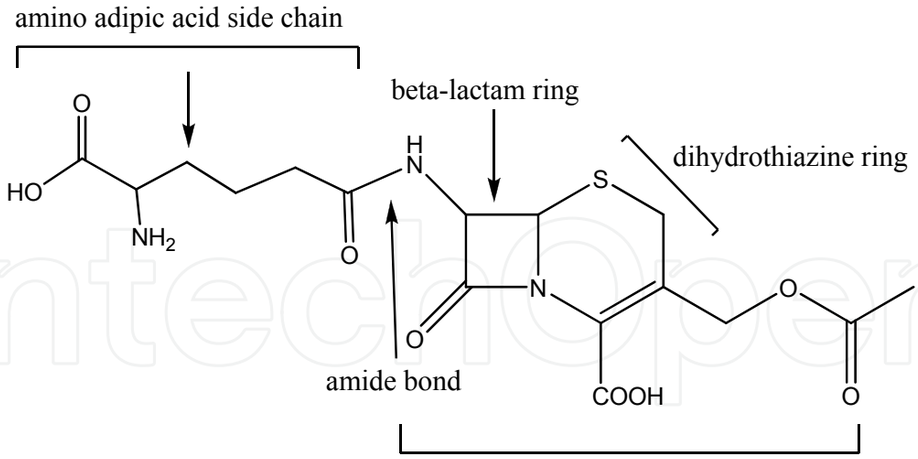
amino group of a double ring nucleus (Figure 1). The side chain was identical to that of penicillin N, *i.e.* D-α-aminoadipic acid. Although both the types have the four membered β-lactam group, cephalosporin-C have a six membered dihydrothiazine ring in place of the five membered thiazolidine ring system which is a characteristic of penicillins. But these antibiotics are not that effective to be used for clinical purposes. The cephalosporin nucleus, 7-aminocephalosporanic acid (7-ACA) is derived from cephalosporin-C, prove to be more effective. Modification of 7-ACA side chains resulted in the development of newer generations of useful antibiotic agents, which leaded to various generations of cephalosporins.

Antibiotics	**Source**	**Mode of action**
Antibacterial antibiotics		
Bacitracin	*Bacillus subtilis*	Cell-wall synthesis
Cephalosporin	*Cephalosporium sp.*	Cell-wall synthesis
Chloramphenicol	*Streptomyces venezuelae*	Protein synthesis
Cycloserin	*Streptomyces leavendulae*	Cell-wall synthesis
Erythromycin	*Streptomyces erythraeus*	Protein synthesis
Kanamycin	*Streptomyces kanomycetoius*	Protein synthesis
Neomycin	*Streptomyces fradiae*	Protein synthesis
Novobiocin	*Streptomyces* sp.	DNA synthesis
Penicillin	*Penicillium* sp.	Cell-wall synthesis
Polymixin	*Bacillus polymyxa*	Cell membrane
Streptomycin	*Streptomyces griseus*	Protein synthesis
Tetracycline	*Streptomyces aureofaciens*	Protein synthesis
Vancomycin	*Streptomyces orientalis*	Cell-wall synthesis
Antiprotozoan antibiotics		
Fumagilin	*Aspergillus fumigatus*	Protein synthesis
Antifungal antibiotics		
Amphotericin B	*Streptomyces nodosus*	Membrane function
Cycloheximide	*Streptomyces griseus*	Protein synthesis
Griseofulvin	*Penicillium griseofulvum*	Cell-wall, microtubules
Nystatin	*Streptomyces noursei*	Damages cell-membrane

Table 1. Different mode of activity/ action of major antibiotics. (Gaurav *et al*., 2011)

The β-lactam antibiotics like penicillin, cephalosporins, vancomycin, etc. are specific inhibitor working against bacterial cell wall (peptidoglycan) synthesis but newer strains have β-lactamase activity which destroys most of the β-lactam antibiotics and thus make them resistant to it. However, cephalosporins proved to be more stable to β-lactamase. Cephalosporin-C (CPC) shows similarity to in structure with the penicillins in having an acyl side chain attached to an amino group of a double ring nucleus (Figure 1). The side chain was identical to that of penicillin N, *i.e.* D-α-aminoadipic acid. Although both the types have the four membered β-lactam group, cephalosporin-C have a six membered dihydrothiazine ring in place of the five membered thiazolidine ring system which is a characteristic of penicillins. But these antibiotics are not that effective to be used for clinical purposes. The cephalosporin nucleus, 7- aminocephalosporanic acid (7-ACA) is derived from cephalosporin-C, prove to be more effective. Modification of 7-ACA side chains resulted in the development of newer generations of useful antibiotic agents, which leaded to various generations of cephalosporins.



Cephalosporin C

Fig. 1. The structure of Cephalosporin

Cephalosporins are nowadays more suggested for the prophylaxis and treatment of bacterial infections caused by susceptible microorganisms. First generation cephalosporins are predominantly effective against gram positive bacteria and successive generations (Table 2) have further enhanced the activity against the gram negative bacteria too (Essack, 2001) However, the synthesis of different generations of cephalosporins are only possible either by microbial routes or by enzymatically converting cephalosporin-C. Hence, a brief discussion on microbial synthesis of cephalosporin-C is quite needed.

Various Generation	Example
First generation Cephalosporins	Cephalothin
	Cephaloridine
	Cephazolin
	Cephradine
	Cefroxadine
Second generation Cephalosporins	Cephamandole
	Cefuroime
	Ceforanide
	Cefotiam
Third generation Cephalosporins	Cefotaxime
	Ceftazidime
	Ceftizoxime
	Ceftriaxone
	Cefixime
	Ceftibuten
Fourth generation Cephalosporins	Cefipime
	Cefpirome

Table 2. Various Generations of Cephalosporin group of antibiotics

2. Microbial synthesis of cephalosporin-C

The biosynthesis of cephalosporin-C is carried only by few microorganisms, viz. fungi, *Streptomyces* sp. and bacteria. It can produced by free and immobilized microbial cells (Kundu *et al*., 2000) using various cultivation modes of batch and continuous strategy (Mahapatra *et al*., 2002). In batch mode of fermentation, Cephalosporin-C is produced in stirred tank bioreactors (Srivastava *et.al*, 1996) as well as in air lift bioreactor (Srivastava *et al*., 1995; 1999).In continuous mode of fermentation, it can be produced both by packed bed bioreactor using different types of immobilization processes and in continuous stirred tank bioreactor. As it's a highly aerobic process in nature, cephalosporin-C is also produced by immobilized microbial cells utilizing symbiotic mode (*in-situ* oxygen production) in a packed bed bioreactor. (Kundu *et al*., 1993)

In order to fulfill the need of large quantity of semi-synthetic cephalosporin, the key intermediates should be produced in large quantity through very efficient and cheap production routes. But the chemical production of the intermediates generates large quantities of wastes and requires expensive and hazardous chemicals and reaction conditions. In order to overcome these problems, enzymes are used to perform the required reactions. Cephalosporin C is converted to 7-ACA in a two step enzymatic process. First the side chain is deaminated by a D-amino oxidase, resulting in an α-keto acid that spontaneously loses carbon dioxide in the presence of hydrogen peroxide to form glutaryl-7-ACA. Subsequent enzymztic deacylation of the glutaryl side chain yields 7-ACA. The enzyme used, cephalosporin acylase, removes a charged aliphatic side chain without damaging the β- lactam nucleus. These enzymatic processes have the advantage of generating less waste and requiring less expensive chemicals. Thus, cephalosporin-C is directly converted to 7-ACA by cephalosporin-C acylase enzyme. (Zhang and Xu, 1993)

2.1 Production strategy of cephalosporin C (primary precursor)

Microbial production of Cephalosporin C, a secondary metabolite, occurs in late stationary phase (Idio-phase) of growth. So the main strategy of the production is to grow the culture to saturation level and then control the flow of nutrient to maintain the stationary phase. (Srivastava *et al*., 2006) Cephalosporin C fermentation always requires highly aerobic condition to maintain uniform yield. Hence, maximum focus is given on oxygenation of the media. There are different processes involved using various modes of bioreactors, *viz.* conventional and non conventional Bioreactors. The conventional mode of bioreactors involves in batch or continuous stirred tank bioreactors whereas non conventional mode involves in packed bed bioreactors, airlift bioreactors and the like. (Srivastava *et al*., 1996)

2.1.1 Cephalosporin C production by conventional mode of bioreactors

Conventional mode involves production by batch bioreactor or continuous stirred tank reactor (Kundu et al., 1993). Surface liquid culture and solid state fermentation are not very much favorable as there is high probability of oxygen limitation. There are some research occurring in the field but the stable process involved is the stirred tank batch bioreactors. They have special attachment for oxygen sparging and agitation for making the oxygen more available to microorganisms (Srivastava *et al*., 1996).The morphological characteristics of the mold change under high agitation which in turn affects the yield of the Cephalosporin C. (Kundu et al., 1993)

Continuous mode involves various continuous stirred tank bioreactors. The first type is where the oxygen is being sparged in the reactor fitted with an agitator (Figure 2 A). The second process involves addition of highly oxygenated media in the bioreactor (Figure 2 B). The continuous processes have advantages but there are several parameters which are to be maintained. Due to the microorganism, being filamentous and taking long time to reach stationary phase microorganism are first allowed to grow under batch condition and then continuous mode of operation is started. (Srivastava *et al*., 2006)

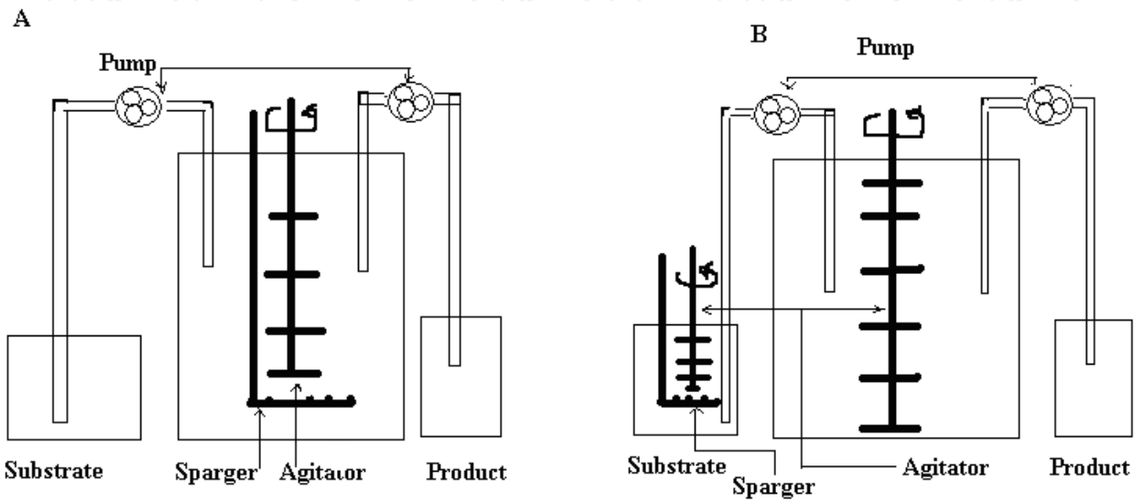


Fig. 2. A) Continuous Bioreactor with oxygen Sparger B) Continuous Bioreactor with oxygen enriched fresh substrate

2.1.2 Cephalosporin C production by Non conventional mode of bioreactors

The non conventional mode involves in either Packed bed bioreactor or Airlift bioreactor. Various modes of immobilized microorganisms are used in packed bed reactors. The main advantage of packed bed reactor is that it can be operated in batch or continuous mode. The residence time and microorganism reusability is high in case of packed bed reactors. There are reported studies involving silk sachets for holding the immobilized beads with significant increase in production. (Kundu et al., 2000)

Cephalosporin C fermentation is a highly aerobic process. The major problem which arises with aerobic fermentation are the mass transfer limitation of oxygen to immobilized cell. (Mishra *et al*., 2005) Even with addition of highly oxygenated media, the beads packed in depth doesn't have enough oxygen to carry out cephalosporin C production, instead they produce Penicillin N, which is not desirable. There is a reported study where mixed culture technique for improving the oxygen supply to the immobilized cells. In such system, the products of metabolism of one microorganism are utilized by the second microorganism. Photoautotrophic algae (*Chlorella* sp.) which produce oxygen *in situ* are coupled with fungi (*Cephalosporium acremonium*) which in turn produce the Cephalosporin C. (Figure 3) (Kundu and Mahapatra, 1993; Kundu *et al*., 2003) The algae absorb CO_2 from air and media producing free oxygen which not only removes the anaerobic condition prevailing in packed bed reactor but also adds up oxygen to the media. Co-immobilization of whole cells were reported to be carried out by using various immobilizing agents, *viz.* Bagasse, Silk

sachets, calcium/Barium/strontium alginate and the same coated with poly-acrylamide resin.

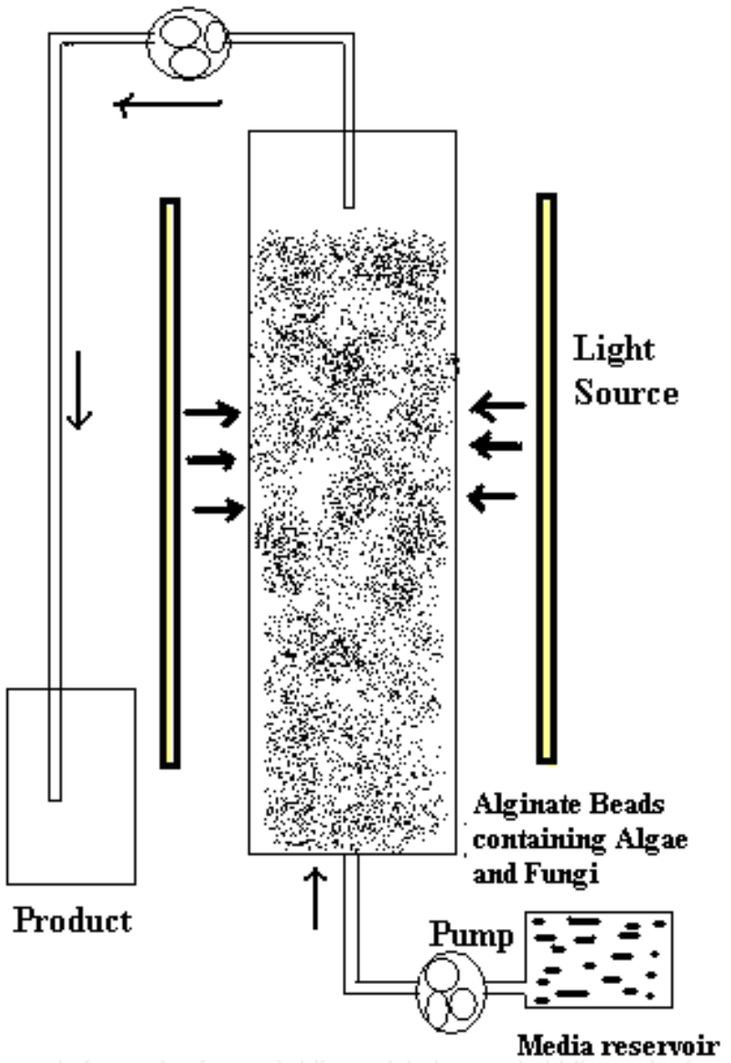


Fig. 3. Packed Bed Reactor with Co-immobilized microbial cells (Algae and Fungi) for enhanced oxygenation

Airlift Bioreactors are the most favorable reactors for production as it completely solve the oxygenation issue. There are two types of Airlift bioreactors. Internal air loop reactors have inner draft tube (Figure 4) while the external bioreactors have external tube as downcomer. They both have significant production values. (Srivastava and Kundu, 1999; Srivastava *et al*., 1995)The air lift reactor ensures proper oxygenation and agitation. They are also gentle on filamentous fungi imparting low shear than any other conventional process agitator, improving production. Though, the process is costlier and tough but it ensures high cephalosporin C production. Figure 4 shows the airlift bioreactors involved in cephalosporin C production. The internal loop airlift reactors have better oxygenation and are preferred above external loop bioreactor.

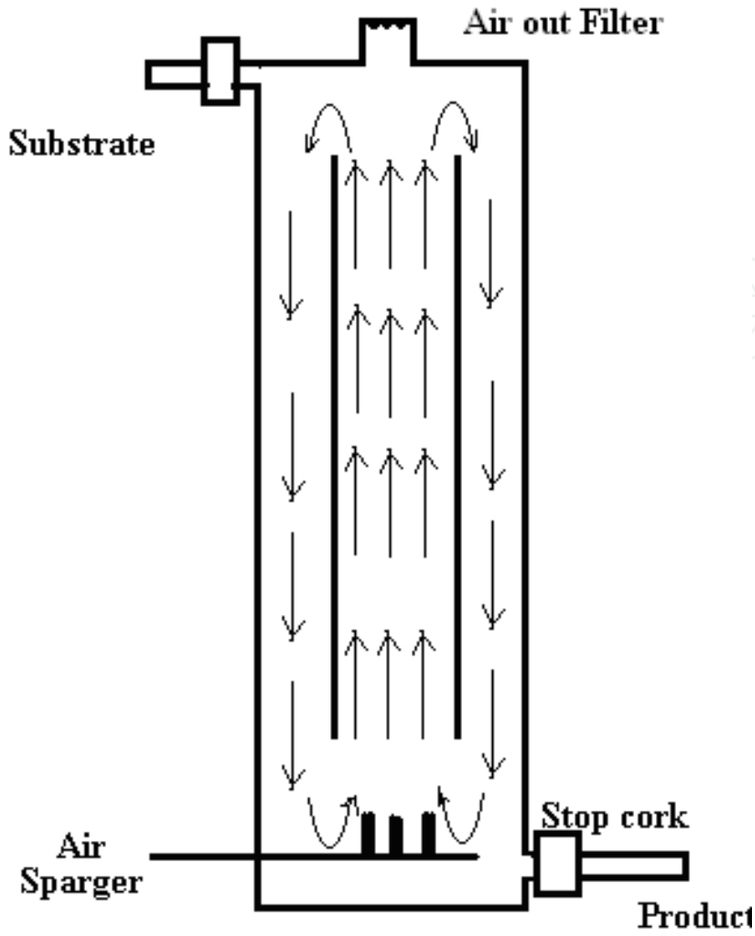


Fig. 4. Internal air-loop reactor for Cephalosporin C production

2.2 Production strategy of 7- amino cephalosporanic acid (secondary precursor)

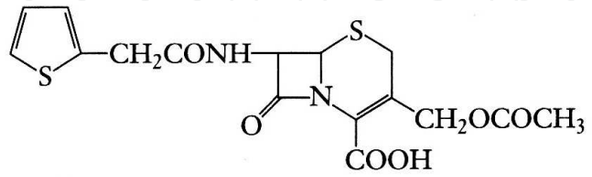
Biosynthesis of 7- Amino cephalosporanic acid (7-ACA) is an important process which involves the use of free and immobilized microbial cells. This can be single step or multi-step microbial enzymatic process (Gaurav *et al*., 2007). There are lots of advantages of single step over the multi-step process (Nigam *et al*., 2005). Cephalosporin C acylase enzyme is involved in the conversion of Cephalosporin C to 7- ACA in single step mode of conversion. The microorganisms used for the synthesis of this enzyme are *Pseudomonas diminuta, Bacillus megaterium* and *E. coli (*Nigam and Kundu, 1999*).* There is also study on continuous production of 7-ACA by loading immobilized microbial cell in a packed bed bioreactor at optimum cells to carrier ratio and at an optimum flow rate (Nigam *et al*., 2005).

3. Different generations Cephalosporins

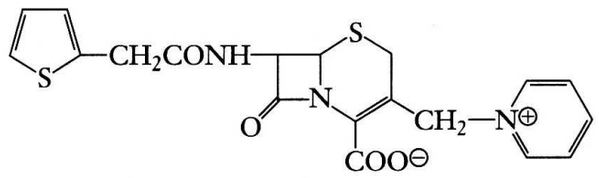
Cephalosporins can usually be classified into four different generations though newer generations are in active research, developed in response to a specific clinical need for a drug with different characteristics than the previous generation. Table 2 narrates the examples of various generation of Cephalosporins group of antibiotics.

3.1 First generation cephalosporins

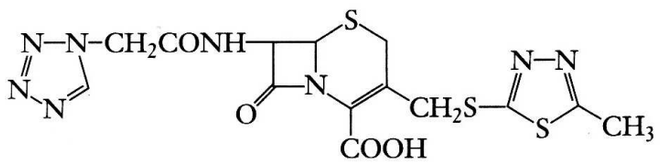
The first generation cephalosporins were first introduced in the mid-1960s and were stable to the β-lactamases known at that time. They permeated the outer membrane of gram-negative bacilli quicker than the penicillins. The first generation drugs include Cephalothin, Cephaloridine and Cefazolin (Figure 5). Cephalothin was synthesized by biochemically using different processing strategies [Gaurav et.al., 2007]. Cephalexin and Cefeclor are both used as oral treatment drugs, and have broad activity against both gram-positive and gram-negative microorganisms. However, they are inactive against *Enterococci* as they don't bind well to PBPs of the *Enterococci* having slight difference.



Cephalothin



Cephaloridine



Cefazolin

Fig. 5. First generation Cephalosporins

3.2 Second generation cephalosporins

The second generation cephalosporins have enhanced activity against gram-negative microorganisms (Livermore 1987; Stan *et al*., 2004). They are more stable to hydrolysis by plasmid-mediated β-lactamases when compared to cefoxitin, to the chromosomal class C cephalosporinase of several *Enterobacteriaceae.* (Medeiros 1997). The second generation cephalosporins include, Cefoxitin, Cefmetazole, Cefuroxime and Cefotetan (Figure 6). Cefuroxime is generally used for respiratory tract and community acquired infections. Cefoxitin has an extra methoxy-group that imparts protection against β-lactamase , but with an added disadvantage that it causes induction of the chromosomal β-lactamases in several bacterial organisms (which can be counterproductive). Cefoxitin (as well as Cefotetan) is well effective against *Bacteroides fragilis*, an enteric anaerobe but not against *Pseudomonas* or *Enterobacter* as it can't enter them.

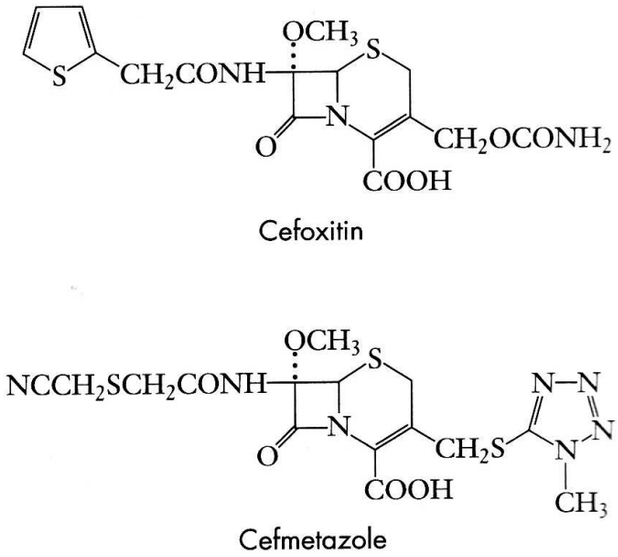


Fig. 6. Second generation Cephalosporins

3.3 Third generation cephalosporins

The third generation cephalosporins are less effective than the first generation cephalosporins against gram-positive cocci but are very much potent against *Enterobacteriaceae,* including the β-lactamase-producing strains (Mandell & Sande 1991). The aminothiazolyl and iminomethoxy groups are the substituents in third generation cephalosporins (Neu 1986), which imparted greater stability against the chromosomal class C β-lactamases and with an increased spectrum of activity.These cephalosporins include Cefotaxime, Ceftizoxime and Ceftazidime (Figure 7). The drugs are broad spectrum antibiotics that are effective against both gram-negative and gram-positive microorganisms. The sodium salts of these antibiotics also showed a greater potential.

Cefotaxime has an enhanced affinity to penicillin binding proteins (PBPs) of gram-negative bacteria and thus it could penetrate faster into bacterial cell as compared to older generation cephalosporins.

Also, cefotaxime is the main intermediary in the synthesis of cefpodoxime proxetil, a third generation oral cephalosporin, introduced recently into medical practice (Durckheimer *et al.*, 1985; Reynolds 1989). Third-generation cephalosporins have a broad spectrum of antimicrobial activity including Gram-positive, Gram-negative, and selected anaerobic species. (Neu 1991).

β -lactamase induction or resistant organism selections are an important issue, especially in nosocomial infections (Stratton *et al.*, 1992). Third generation cephalosporins vary in their ability to induce β-lactamases, but none is as effective inducers as the cephamycins, clavams, or carbapenems The discovery of *Klebsiella* isolates resistant to oxyiminocephalosporins imparted more difficulties to β-lactam antibiotics mediated by extended-spectrum β-lactamases (ESBLs). Mutation in the structural genes of plasmid-mediated TEM, SHV, and OXA β-lactamases and to a lesser extent in the PER and CTX enzymes enhanced their affinity for third generation cephalosporins and monobactams, but with varying degrees marking the pavement for newer generations.

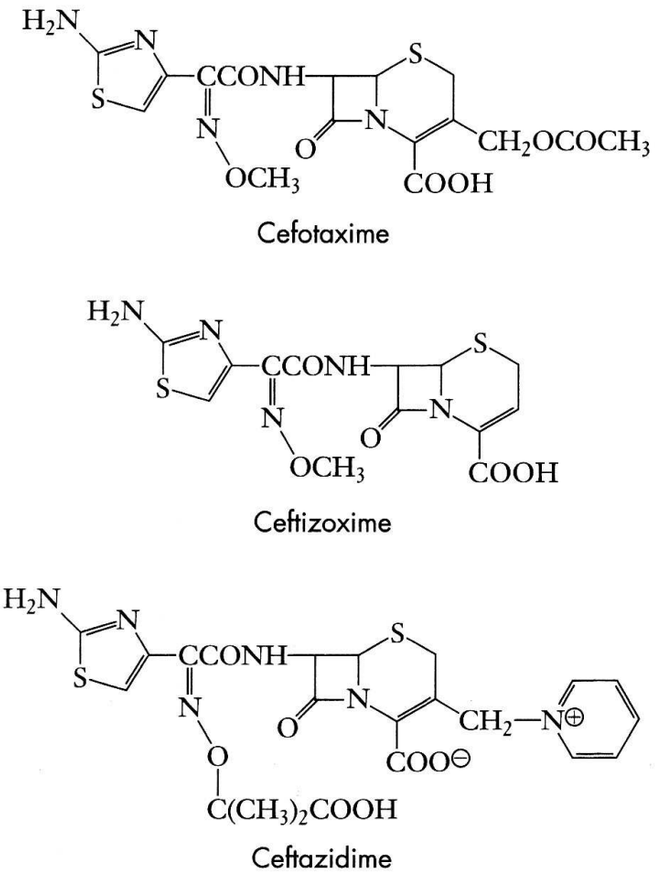
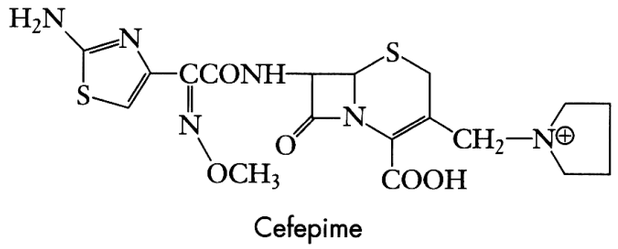


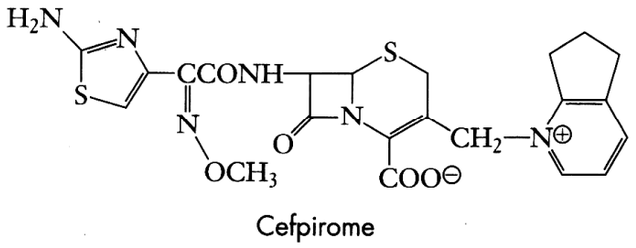
Fig. 7. Third generation cephalosporins

3.4 Fourth generation cephalosporins

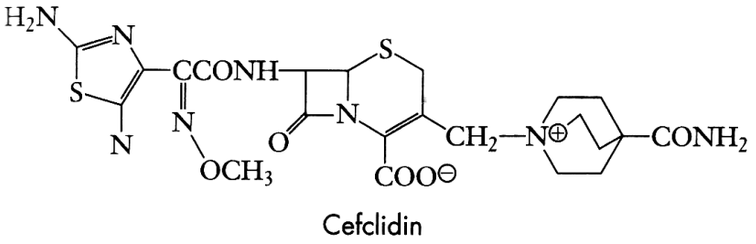
The fourth generation cephalosporins contains a positively charged quaternary nitrogen atom at C-3, resulting in higher activity (compared to the third-generation cephalosporins) against β-lactamase derepressed mutants of *P. areuginosa* and other enteric bacteria (Georgopapdakau *et al*., 1989). The fourth generation cephalosporins, Cefepime, Cefpirome and Cefclidin (Figure 8) have the 7-amino-thiazolyl groups [(Livermore & Williams 1996). Cefepime have good potency against gram-negative organisms such as *Pseudomonas aeruginosa*, and gram-positive organism such as *Staphylococcus aureus*, also exhibiting increased stability against β-lactamase-overproducing bacteria. Cefepime is [6 R – [6 α, 7 β (Z)]]-1-[[7-[[(2-amino-4-thiazolyl) (methoxyimino) acetyl] amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo oct-2-en-3yl] methyl]-1-methylpyrrolidinium inner salt. It is synthesized from 7-aminocephalosporanic acid (7-ACA) with help of trimethylsilyl iodide and N-methylpyrrolidine. It is stable to hydrolysis by the more common chromosomal and plasmid-mediated β-lactamases, and it is quite stable against inducible chromosomally mediated cephalosporinases



Cefepime



Cefpirome

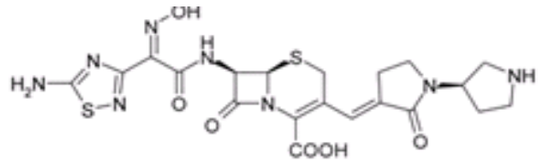


Cefclidin

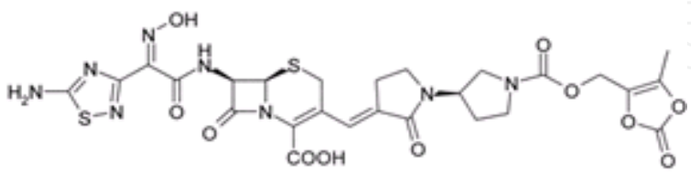
Fig. 8. Fourth generation Cephalosporins

3.5 Fifth generation cephalosporins

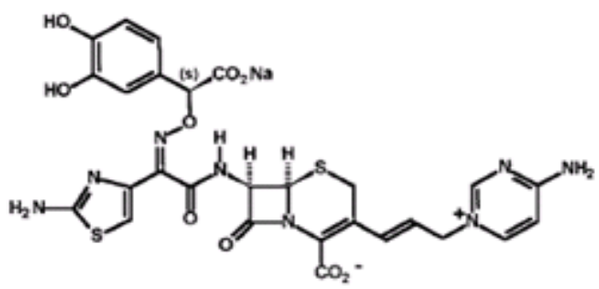
The fifth generation cephalosporin is still an unclear picture with many new modified cephalosporins in the research sector. This generation antibiotic is specifically developed against nosocomial infections of MRSA and Pseudomonas based refractory infection in immuno-compromised patients. Drugs which are in immediate attention of FDA are Ceftobiprole, LB10522 (Kim et al., 1996) and RU-59863 (Figure 9). Ceftobiprole specifically attacks by binding to this penicillin-resistant target. Interactions with cephalosporin side chains occurs in the groove, closed in the free PBP 2a enzyme, binds to the 7-acyl amino side chain, and in another extended groove where it interacts with the 3'-cephem side chain through noncovalent interactions (Lim & Strynadka 2002). It is stable to class A penicillinases produced by *S. aureus* and enteric gram-negative microorganisms and is more stable to few class C beta-lactamases of enteric gram-negative microorganisms (Hebeisen *et al*., 2001).



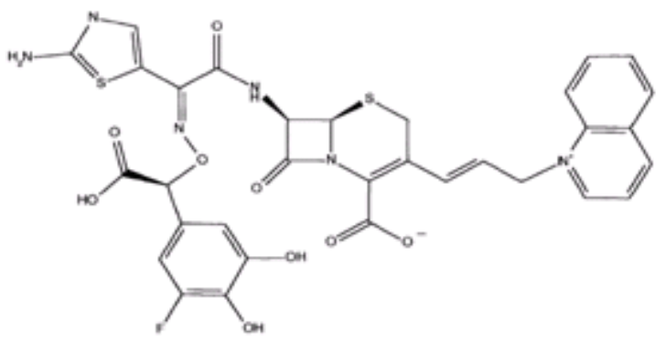
Ceftobiprole



Ceftobiprole medocaril



LB10522



RU-59863

Fig. 9. Fifth generation Cephalosporins

4. Current research in new generation cephalosporins

It is also known that incorporation of a methoxy group in both cephalosporin and penicillin has led to a considerable increase in beta-lactamase stability. These findings prompted us to prepare methoxy and formamido derivatives of Cephalosporin and screen them for their antibacterial activity.

Our research team's current work is to attempt synthesizing some new semi-synthetic cephalosporins and some by modifying already existing semi-synthetic cephalosporins such as cefotaxime (third generation). It is broad spectrum antibiotic with high resistance against beta-lactamases. But the main problem is that it is poorly soluble in water. Hence, the efforts have been made to prepare cephalosporins having better solubility using cefotaxime. All these semi-synthetic cephalosporins are derived from the key intermediate 7- ACA, a product derived from cephalosporin C hydrolysis. They differ in the nature of the substitute attached at the 3 and/ or 7- position of the cephem ring and express various biological and pharmacological effects.

In the present work, enzymatic method has been employed to produce 7-ACA, the key intermediate and this 7-ACA is then utilized for the synthesis of new semi-synthetic cephalosporins. Nicotinic acid, benzimidazole, imidazole or substituted benzimidazole system has been shown to have different pharmacological effects including antifungal, antibacterial and antiviral effects. 2-substituted benzimidazoles, with various types of biological activity, have a close relationship to nucleic acid metabolism. Hence, semi-synthetic cephalosporins containing these nucleuses were prepared and the assessment of these molecules has been checked to interfere with various cellular and metabolic processes. (Figure 10)

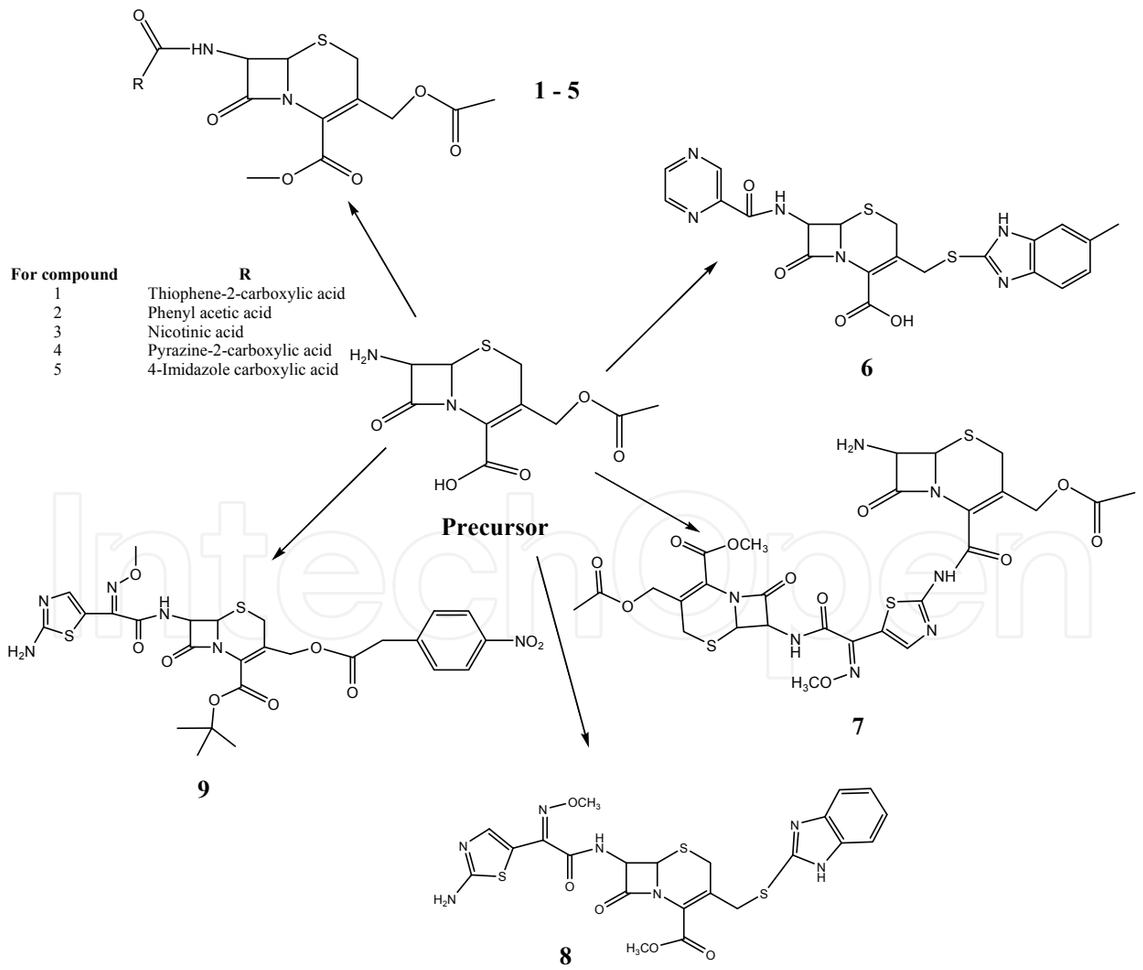


Fig. 10. Formation of new generation Cephalosporins.

In a search for unique and potent cephalosporin antibiotics, we have prepared new semi-synthetic cephalosporins. The motivation for synthesizing these semi-synthetic cephalosporins was to increase the availability of drug at the target site and their oral absorptivity and increased stability. Thus, recurring need for an easily cleaved blocking group for the carboxylic acid in the cephalosporin synthetic chemistry forms the basis of the research. All the synthesised cephalosporins were having easily hydrolysable esters for oral absorption studies; they were also having such suitable blocking groups for the carboxyl, which might be removed later without disruption of the beta-lactam ring. Although simple esters, like the methyl ester, are known to possess diminished antibiotic activity compared to the free acids, the possibility exists that more easily hydrolysable esters (by enzymatic or chemical means) might exhibit significant in vivo activity. A therapeutic advantage might be anticipated from derived compounds if the structural environment of the carboxyl group is a bar to absorption through the gastric or intestinal walls. Activity could be inherent in the derivative or be produced a result of enzymatic cleavage to the parent compound after absorption has occurred. Gastric acidity, often a negative influence in oral absorptibility of penicillins, would send to be an unlikely factor in cephalosporin absorption because of the relatively good acid stability of this class of antibiotics. For the synthesis of these analogues, the methods that are of general applicability are used. To form peptides from a cephalosporin required that the carboxyl at C-4 be appropriately activated for acylation of a protected amino acid. In synthetic organic chemistry, compound containing the carbodiimide functionality are dehydrating agents and are often used to activate carboxylic acids towards amide or ester formation. Additives, such as N-hydroxybenzotriazole are often added to increase yields and decrease side reactions. EDC (acronym for 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride) is a water soluble carbodiimide which is used as a carboxyl activating agent for the coupling of primary amines to yield amide bonds. The possibility that amides derived from a cephalosporanic acid and an amino acid might cross the intestinal wall and be cleaved in the body.

5. Conclusion

In general, attempts to modify the β- lactam thiazolidine ring system of penicillin without loss of antibacterial activity had been unsuccessful. The discovery, structure elucidation and modification of cephalosporin C, which led to important new generations of Cephalosporin group of antibiotics and its large scale production and marketing. In the past decade, even though cephalosporin antibiotics have made remarkable progress and contribution in the treatment of acute disease, many efforts still exist to achieve the well-balanced broad-spectrum and to improve beta-lactamases stability. This work, lead to highly active, acid stable, penicillin resistant, nontoxic antibiotic with increased potency against a wide range of bacteria. Although the progress is in preliminary stage but significance of the work is enormous.

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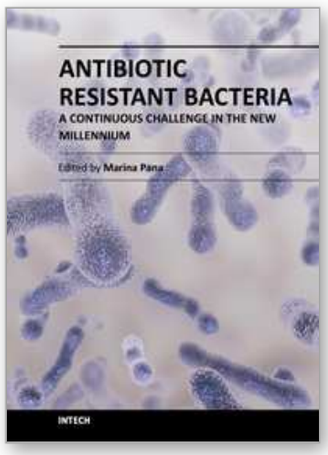

Antibiotic Resistant Bacteria - A Continuous Challenge in the New Millennium

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Antibiotic-resistant bacterial strains remain a major global threat, despite the prevention, diagnosis and antibiotherapy, which have improved considerably. In this thematic issue, the scientists present their results of accomplished studies, in order to provide an updated overview of scientific information and also, to exchange views on new strategies for interventions in antibiotic-resistant bacterial strains cases and outbreaks. As a consequence, the recently developed techniques in this field will contribute to a considerable progress in medical research.

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