

**Historical Review of the Penicillin and Related Compounds ( $\beta$  – Lactams)****Luma Salman Abd***\*Department of chemistry- Faculty of Science – Diyala – Univ.**Lum20072001@yahoo.com*DOI: <https://doi.org/10.32947/ajps.18.01.0367>**Abstract:**

In spite of the old age of beta lactam, they continue to provide good health and preventing human diseases by virtue of industrial production and discoveries of small new beta-lactam group of secondary metabolites. Antibiotic resistance in bacteria has become a serious problem worldwide therefore, the present survey discusses the event that occurred in the progress of the penicillin, and beta-lactam from discovery to implementation as a therapeutic agent in order to overcome this issue. Moreover, this review provides a descriptive overview of the various published ways to enhance the clinical effectiveness of beta-lactam antibiotics and the methods that lead to synthesis of beta-lactam ring.

**Key words:** Penicillin, beta-lactam antibiotics, antibiotic resistance

مراجعة تاريخية للبنسلين والمركبات ذات الصلة ( البيتا لاكتم)

**الخلاصة:**

تعتبر مضادات البيتا لاكتم من المضادات الحيوية الواسعة الانتشار قديما وما زالت تحتل المرتبة الاولى في معالجة عدد كبير من اسباب العدوى الجرثومية والبكتيرية بسبب تطور الانتاج الصناعي في هذا المجال او بسبب البحث الدائم عن الكائنات الحية التي تحتوي على هذا الصنف مع اجزاء اكثر نشاطا. مقاومة البكتيرية لانواع مختلفة من المضادات الحيوية أصبحت من المشاكل التي يعاني منها العالم لذلك هدف البحث إلى تسليط الضوء على مراحل التطور التي شهدتها المضادات الحيوية التي تحتوي على حلقة البيتا لاكتم من اجل التغلب على هذه المشكلة بالإضافة إلى هذا استعرض البحث البحوث المنشورة عالميا التي تناولت التقنيات الحديثة والمتطورة لزيادة فعالية هذا الصنف من المركبات كما استعرض هذا البحث بعض من الطرق الخاصة بتحضير حلقة البيتا لاكتم.

الكلمات الرئيسية: البنسلين، البيتا لاكتم، مقاومة المضادات الحيوية

**Introduction:**

In August 1928, Alexander Fleming discovered accidentally the first antibiotic, which played an important role throughout the world in treating and preventing human diseases.<sup>[1], [2], [3]</sup> After one year, Fleming published his discovery in the British Journal of Experimental pathology, but his findings received no attention.<sup>[2], [4]</sup> Because of the difficult isolation and characterization as Fleming was bacteriologist, not a chemist hence Fleming was speaking to other scientists<sup>[2], [4]</sup> among them, Harold King Head of the Department of Chemistry at the Medical Research, but little help was provided Fleming. In 1932, Harold Raistrick, a professor of biochemistry at the London School of Hygiene Tropical medicine, took the substrate (penicillin) and sent it to Charles Thom in the u.s. Department of Agriculture who confirmed

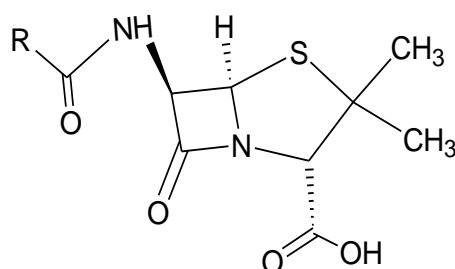
instability of penicillin during purifying. Then his efforts turn to the isolation of the inert pigment from the mold with the assistance of bacteriologist, R-Lovell and chemist, p.w. clutter buck. As a result of this work was substance but, not antibacterial. In 1935, international congress of physiologists in Leningrad, reported that penicillin for therapeutic uses impossible.<sup>[2], [4]</sup> The most important work was in 1939 when a team of researchers (Florey, Chain and Heatley, Oxford Uni.) has developed method to purified penicillin.<sup>[2], [4]</sup> Despite of the differences of personality and their scientific back ground, they managed to work together toward a common aim. Heatley was responsible for growing the mold and Chain for extracting penicillin from the broth, whereas Florey was responsible for animal trials<sup>[2], [4]</sup> On 25 of

the May 1939, the group applied the project on eight mice. Four of them were injected with penicillin, and the rest of mice was kept as control without any treatment. The result was convincing, and only the control group was died. In 1940, Lancet published a paper described the effect of penicillin on two kinds of bacteria in mice<sup>[2], [4]</sup>

### Development of beta lactam

Since discovery the penicillin in 1928 Figure-1.<sup>[5]</sup> The patient began using it as therapeutic product to treat infections in during World War II in 1942.<sup>[1], [2]</sup> The

research on penicillin show it was nontoxic to animals in large doses, efficient antiseptic for application or injection into areas infected and the substance was active against two kinds of bacteria for instant, Diphtheria bacilli and pyogenic cocci where as other bacteria such as the coli typhoid group and the enterococcus were insensitive.<sup>[1], [6]</sup> The chemical structure of penicillin and its families having four-membered  $\beta$ -Lactam ring fused to a five membered thiazolidine ring causes the  $\beta$ -Lactam ring more reactive against virus kinds of bacterial infections.<sup>[7]</sup>

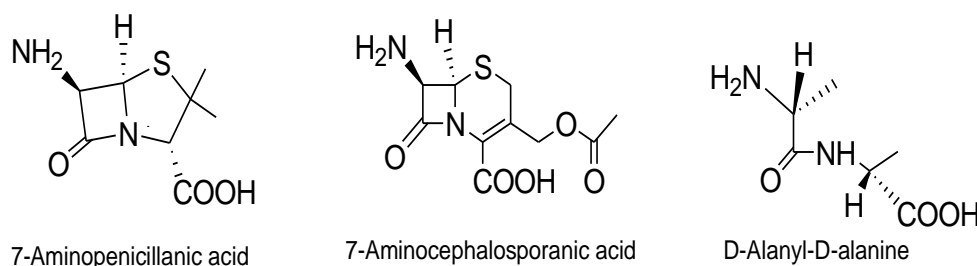


**Figure (1): Bicyclic Penicillin structure, R= is the variable group, Formula C<sub>9</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub>S**

increasing bacterial resistance of penicillin encouraged research to develop newer antibiotics with an alternative mechanism of action.<sup>[7]</sup>

It was found that 6-aminopenicillanic acid (6-APA) Figure (2) was the key step in the synthesis and semi-synthesis of penicillin consequently novel beta-lactam could be

produced by adding unusual side chains to 6-APA.<sup>[2]</sup> Carbenicillin was the first compound introduced by semi-synthetic method against *P.aeruginosa*. A new family of beta-lactam antibiotic have been synthesized using 7-ACA as the precursor of generation of cephalosporins with broad spectrum activity<sup>[2] [8] [9]</sup> Figure -2.



**Figure (2): Molecular structure of the precursor for semi-synthetic  $\beta$ -lactam compounds**

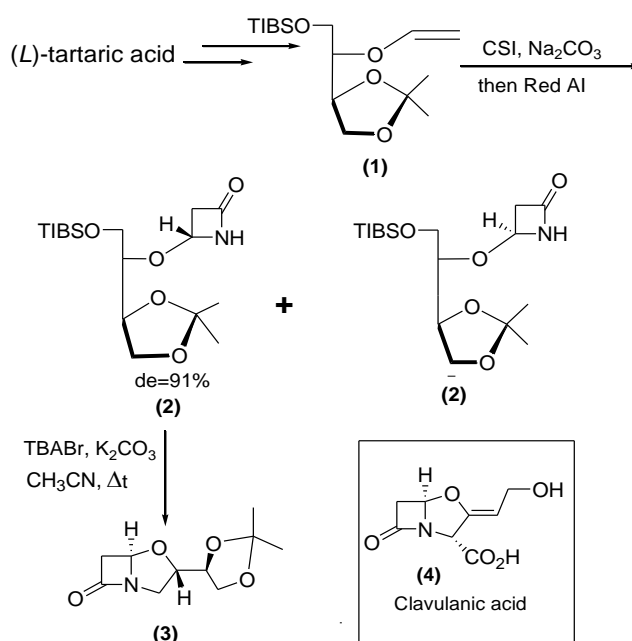
This short review will focus on the development of synthesis methods to generate new members of beta-lactam antibiotics that processing novel structure and antibiotics properties against drug-resistant bacteria.

In 2004, Chmielewski et al<sup>[10]</sup> have reported several methods for the preparation of oxygen analogues of penicillin and cephalosporin. Five synthesis methods have been used to build basic skeletons of clavams and 5-

oxacephams. Three of the synthesis methods depended on the nucleophilic substitution at C-4 of the azetidine 2-ones as intra or intermolecular process. The remaining two involve of cycloaddition reaction between ketenes and iminoethyl or between vinyl ether and isocyanates. According to Chmielewski, et al, all methods were focused on the stereo control of R- configuration of the bridgehead carbon atom linked to the oxygen and nitrogen atoms and on the relative cis configuration of vicinal protons of the beta lactam ring.

The [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) to vinyl ethers was the best method to introduce the four-member ring  $\beta$ -Lactam Scheme-1. The synthesis route started from L-tartaric acid to introduce vinyl ether (1) Reaction of vinyl ether (1) with (CSI) produce of  $\beta$ -Lactam (2) in diastereomeric excess(de)=91%.

Alkylation of the nitrogen atom in (2) yielded clavam (3) which is structurally related to the natural antifungal compound clavulanic acid (4) has showed excellent activity as an inhibitor of  $\beta$ -Lactamase enzymes.



**Scheme-1: Synthesis of clavam**

In 2011, Kardos <sup>[6]</sup> reported about the development of  $\beta$ -Lactam and other classes of antibiotics over the years in order to overcome the resistance to penicillin. Two evolutions occurred which led to reuse the penicillin confidently, one was the isolation of compound 6-amino penicillanic acid (6-APA) which then used in the semi-synthesis of penicillin that has broad-spectrum antibacterial activity and resistance properties to acid and penicillinase.

The second, discovery was commercial cephalosporin N, which was then renamed penicillin N. Penicillin N showed activity against both Gram-positive and Gram-

negative bacteria. Comparison to penicillin G, the original penicillin found in 1928, it was only had 1% of activity against Gram-positive, but had greater activity against Gram-negative bacteria. The hydrophilic nature of penicillin N due to the carboxyl group in the side chain and it is approximately equivalent activity against Gram-positive and Gram-negative bacteria led to never used it as commercial antibiotic.

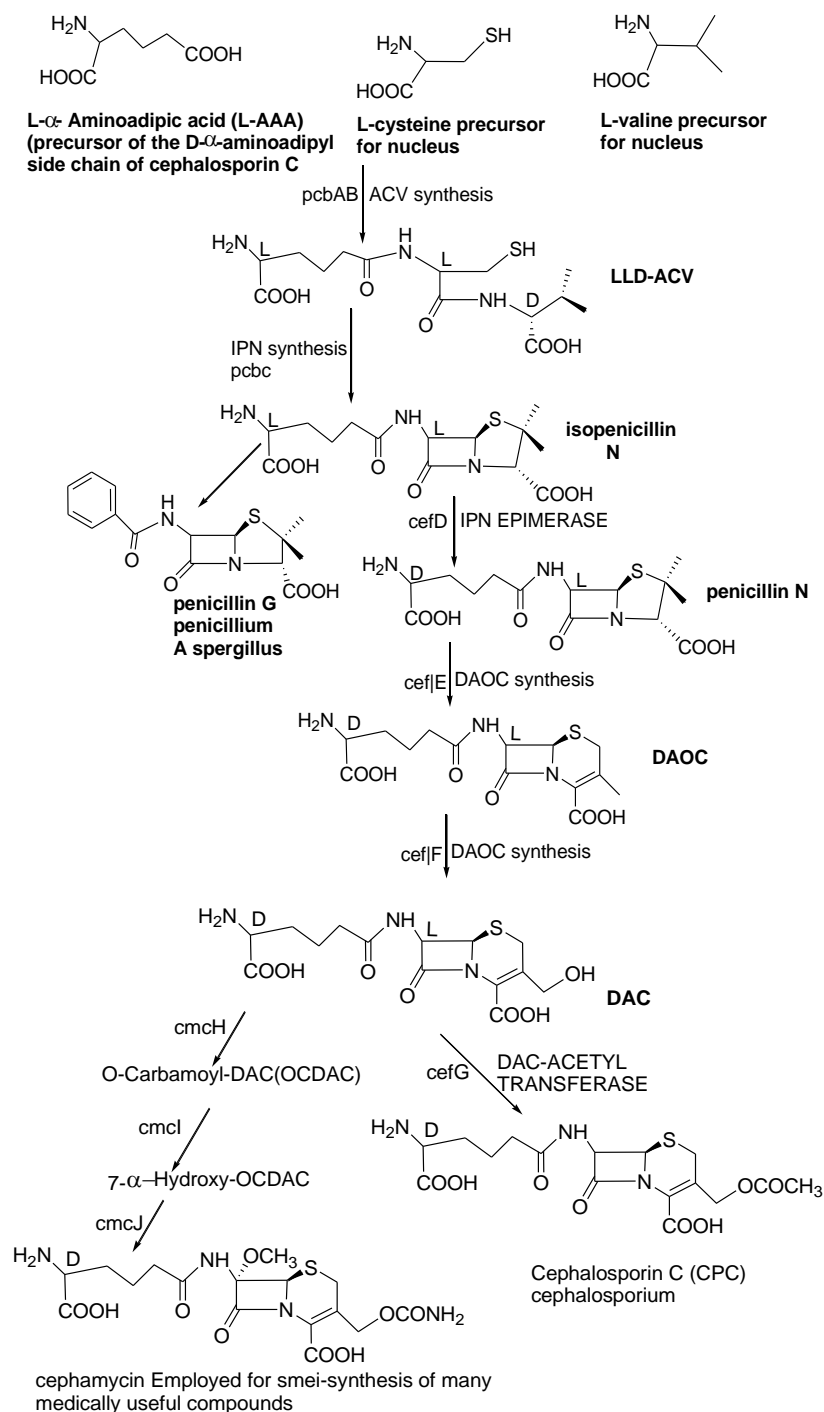
Kardos *et al* <sup>[6]</sup> and Ozcengiz <sup>[11]</sup> had also described the other four newer  $\beta$ -lactams. Using additional acyl groups as side-chain precursor other than phenylacetic acid for penicillin G produce new  $\beta$ -lactam and one

of them, penicillin V (ph. exonym ethyl penicillin), that used as commercial application because of its stability to acid hydrolysis which permitted oral administration therefore penicillin V and G (benzyl penicillin) became the main penicillin of commerce.

It is worth to note <sup>[6]</sup> that cephalosporin P was not a  $\beta$ -lactam and found to be of steroidal nature. The modified new  $\beta$ -lactams were found to be related to penicillin N that consisted of six-member dihydrodiazepin  $\beta$ -lactam ring in place of the five-member thiazolidine of  $\beta$ -lactam ring. It was then called cephalosporin C. The nucleus of penicillin C was named 7-aminocephalosporanic acid (7-ACA). It strongly absorbed ultraviolet spectrum, non-toxic and stable in acid media.

In spite of penicillin (C and N) were never became commercial, they led to important knowledge on the biosynthesis progress and development of many semi-synthesis steps of these compounds. Despite the stability of cephalosporin C to penicillin  $\beta$ -lactams, the main disadvantage of the compound was its weak activity, it had only 0.1% of the activity of penicillin G against sensitive staphylococci bacteria. Many other new and broad antibacterial cephalosporin were developed by semi-synthetic removal of its D- $\alpha$ -aminoadipic acid side chain and replacement with phenyl-acetic acid, for example, cephalothin, cephaloridine and cephaloglycin <sup>[6]</sup>

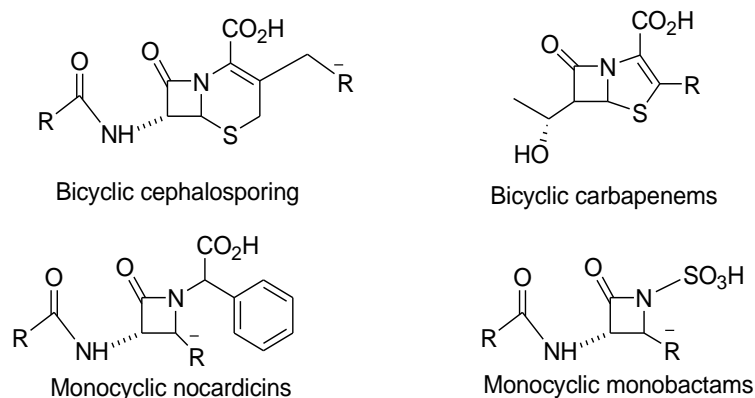
On the other hand, the authors' found that using the ring expansion enzyme provide important tripeptide precursor of all penicillin and cephalosporins, from *A.chrysogenum* for instance  $\beta$ -(L- $\alpha$  amino adipyl) L-cysteinyl-D- Valine ( LLD-ACV). The key step was the enzyme ACV synthetase which acting on L- $\alpha$  aminoadipic acid, L-cysteine, and L-valine to give LLD-ACV. In addition, the isolation of pure is penicillin N synthetase (cyclase) that converted the LLD-ACV to is penicillin N. Another important compound recorded in the history development of the  $\beta$ -lactam antibiotic was carbapenems which is similar to penicillin in having a  $\beta$ -lactam ring fused to five-membered ring, but the difference was unsaturated five-member ring and contained a carbon atom instead of sulfur. <sup>[6]</sup> The sulfur atom was present in another location in all carbapenems that were produced by *Streptomyces*'s. A huge numbers of carbapenems were reported, but the most imported one was thienamycin, it has broader spectrum, nontoxic natural antibacterial agent ever found and was relatively resistant to  $\beta$ -lactamases. Also, it is sharing with penicillin in inhibited cell wall synthesis, for these reasons penicillin and cephalosporins became the best therapeutic agent that destroyed a wider range bacteria. The biosynthesis of penicillin and related compound are shown in Figure -3 <sup>[6]</sup>



**Figure (3): Biosynthesis of penicillin's, cephalosporins C and not clinically cephamycin C from its precursors L-cysteine, L-valine and L- $\alpha$ -Amino-adipic acid.**

In 2008, Taros <sup>[12]</sup> reported, the most developed methods that were published to overcome resistance bacteria and enhance the medical properties of  $\beta$ -lactam and their derivatives, beginning with structurally modified penicillin's, new  $\beta$ -lactam with alternative mechanism,

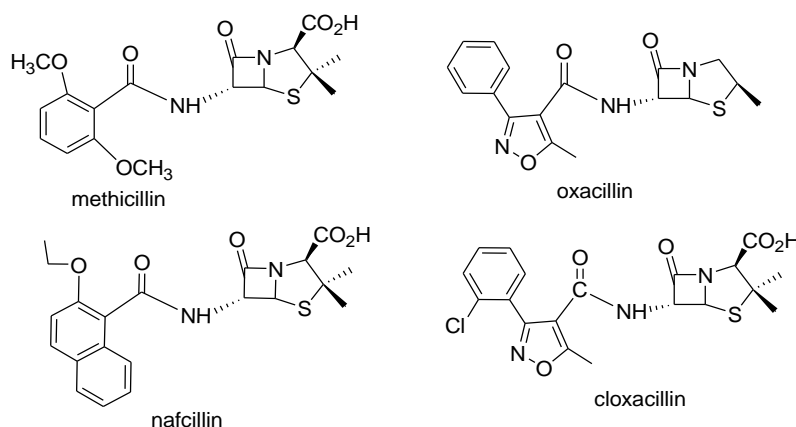
delivery methods such as liposomes nanoparticles and intracellular delivery approaches. Penicillin family consists of four metabolites of which are bicyclic while the other two have monocyclic penicillin Figure -4.



**Figure (4): Penicillin family**

Though the modification of natural product penicillin skeleton that isolated from bacteria or synthesized in the laboratory have shown resist to  $\beta$ -lactamase

hydrolysis Figure (5), but quickly open the way to growth of new pathogenic bacteria having  $\beta$ -lactamase-mediated resistance.



**Figure (5): Modification of natural product penicillin skeleton**

Different approach has been used to combat resistance and recover the anti-microbial activity of antibiotic was combined used of  $\beta$ -lactamase inhibitors with a  $\beta$ -lactam antibiotic, and the base of mechanism was combine the penicillin with in activators clavulanic acid, sulbactam and tazobactam <sup>(13)</sup> and they have been commercially available in amoxicillin-clavulanate, ticarcillin-clavulanate, ampicillin- sulbactam, and piperacillin-tazobactam, as a result increase the activity spectrum of sensible penicillin <sup>[12] [13]</sup>

Amoxicillin with clavulanic acid now be used to treat infections caused by staphylococci and most class A of enzymes  $\beta$ -lactamases; however, these inhibitors

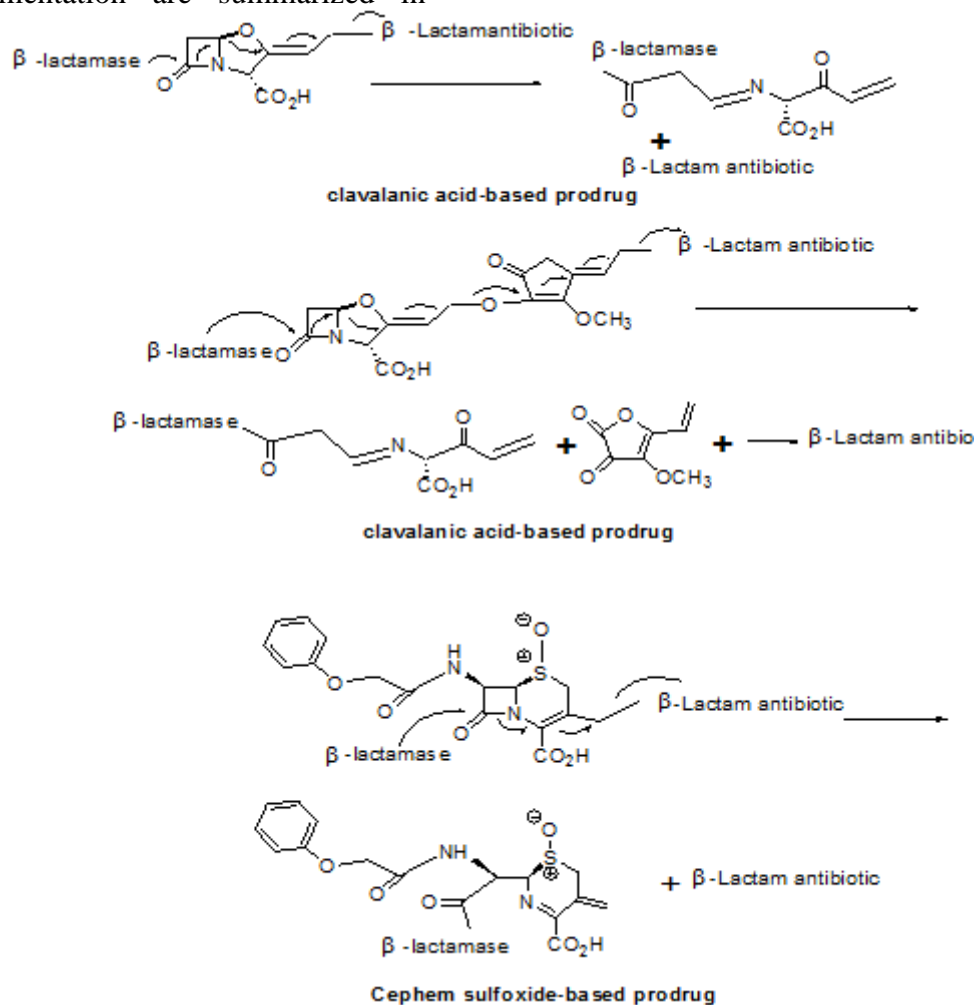
have much less effect on AmpC  $\beta$ -lactamases. <sup>[12], [13]</sup> Production is one of the mechanism of resistance to  $\beta$ -lactamases in enterobacteria, that conferring resistance to all  $\beta$ -lactam, consequently, therapeutic options need for broader -spectrum  $\beta$ -lactamase inhibitors.

On the strategies that authors described was prodrug delivery of  $\beta$ -lactamase which is inactive substance that converted to a drug within the body by the impact of enzymes or other chemicals and as a result alter the physiochemical properties of drug, aqueous solubility, protection against fast metabolism, and carriers transport the compound to specific organs or tissues.

Mechanism of inhibition of  $\beta$ -lactamases by clavulanate and releases the penicillin

cephalosporin antibiotic by subsequent ring fragmentation are summarized in

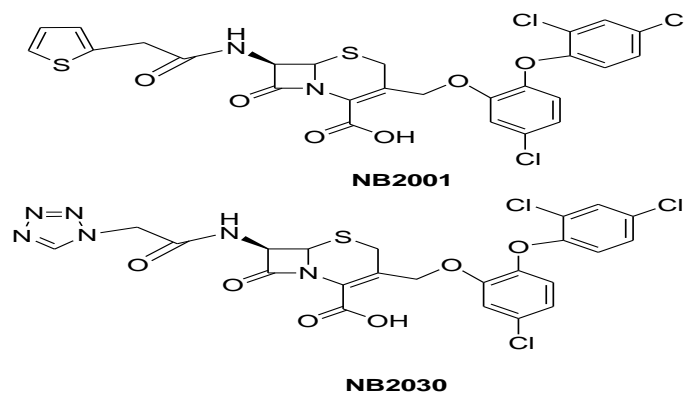
Figure-6. [12]



**Figure (6): Mechanism of three different prodrug delivery system that release active  $\beta$ -lactam in the presence of  $\beta$ -lactamase**

Enzyme-catalyzed therapeutic activation (ECTA) is another approach designed to provide active substrate directly to the resistant bacteria cell. This approach

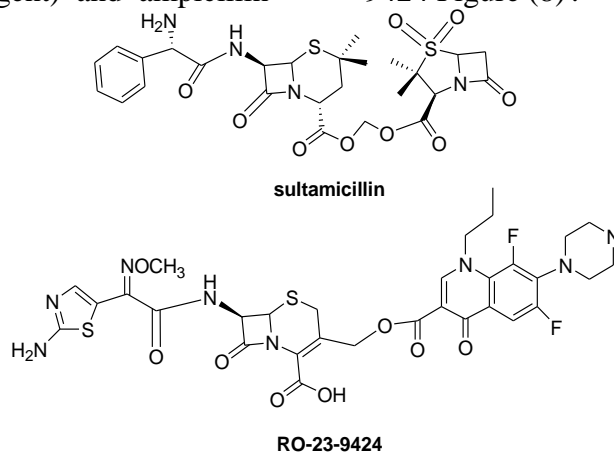
depends on coupling a cytotoxic compound onto a  $\beta$ -lactam skeleton. NB-2001, and NB-2030 are example of this strategic [12] [14] Figure (7)



**Figure (7): Cephalosporin-triclosan dual-action drugs**

Another oral compound is sultamicilline Figure (8) chemically is ox methyl penicillin ate sulfone ester of ampicillin. Conjugate of sulbactam (a semisynthetic  $\beta$ -lactamase inhibitor agent) and ampicillin

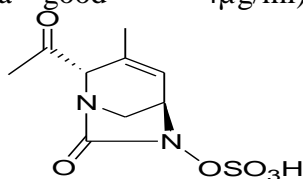
led to extend the activity of ampicillin to  $\beta$ -lactamase<sup>[14]</sup> combination of cephalosporin and fluoroquinolone gave similar mode of action represented by RO-23-9424 Figure (8).<sup>[12]</sup>



**Figure (8): Sultamicillin and Ro-23-9424**

With the same strategy, combination the sulbactam with unsaturated diazabicyclo-octenone ETX2514 showed a good

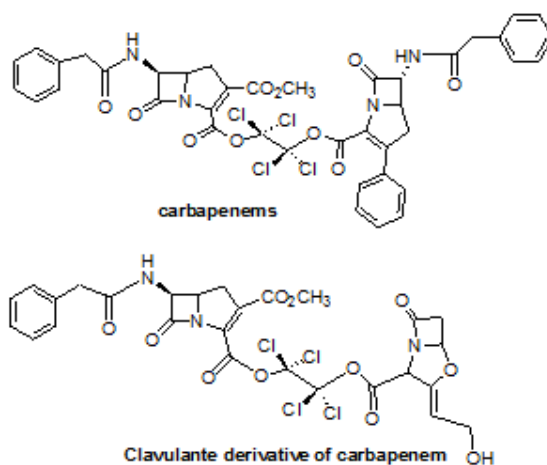
activity against multidrug resistant *Acinetobacter baumannii* with (MIC<sub>90</sub> at 4 $\mu$ g/ml) *in vitro* Figure (9)<sup>[15]</sup>.



**Figure (9): ETX2514**

The dimer of  $\beta$ -lactamase (carbapenem prodrug) afforded a new class of antibiotic

that target both  $\beta$ -lactamase and transpeptidase Figure (10)<sup>[12]</sup>

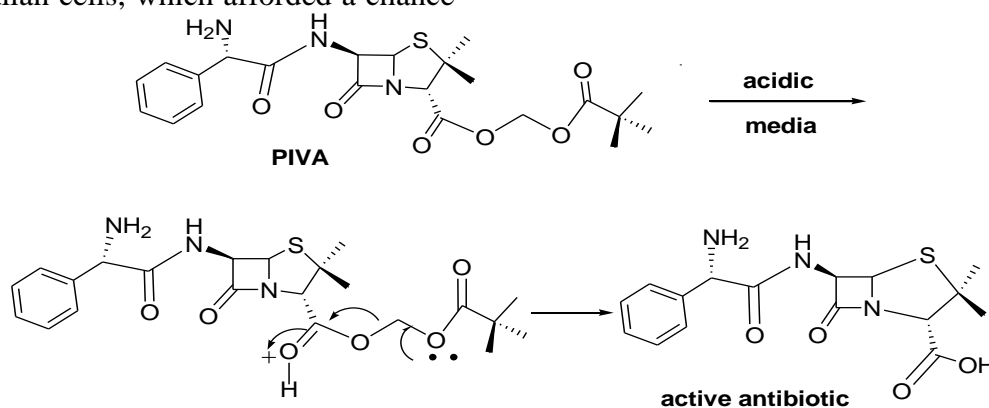


**Figure(10):Dimeric carbapenems and clavuate**



One of the most antibiotic resistance in recent year was intracellular pathogens. This occur when microbes enter mammalian cells, which afforded a chance

for recurring in faction. A prodrug pivaloyloxy methyl ampicillin (PIVA) has been used to delivere into cells Figure (11) [12]



**Figure (11): Acid-promoted cleavage of pivaloyloxymethyl ampicillin**

The active site carboxylic acid is generated after exposure of PIVA to acid, resulting cleavage of ester bond. Pivampicillin compounds show significant antibacterial activity against intracellular *Listeria monocytogenes*, even when  $\beta$ -lactamase was added to the extracellular milieu. Along with drug delivery mechanism the author (12) have also described and investigated of liposomes, nanospheres and Nano capsules as carries of biologically active compounds to infection area. The chemistry of these strategies depends on micron size of these collide and greater mobility in the body and thus better delivered an antibiotic to the target area. Delivery of an antibiotic occurs through endocytosis which follows the initial interaction of the liposome with the cell membrane, either through a mediated or passive fusion of the lipoproteins which releases the desired drug. The main disadvantage of liposomes is uncontrol their stability, however, using variants of pegylated that provide stealth properties and longer serum lifetime made the liposomes highly suitable for antibiotic delivery.

Based on this route, Taros *et al* (12) showed another major sort of drug delivery vehicle. Nanoparticles were the most common type that consist of polymeric systems that from nanospheres in aqueous media in 5-350 nm in diameter. They are

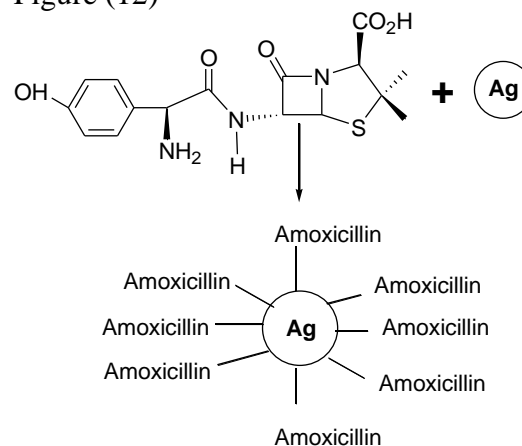
more stable than liposomes in biological fluids and during storage. Nanoparticles are widely used in medical fields due to uniquely small size, oral delivery, quick absorption in the gastrointestinal, protect the drug from degradation while inside. The small size of nanoparticles particularly, <100nm made these compounds unrecognized by the RES, thus, easily reach the bone marrow where as those greater than 300 nm are rapidly picked up by phagocytes and are not able to pass into heart or lung tissue. Most kinds of nanoparticles that were used for antibacterial localized in skin, certain tissues or is systemic are polyacrylates, polylactide-co-glycosides and metal nanoparticles. In 1970s, polymeric nanoparticles have been studied as drug carriers, and since that much research has been carried out to discover and develop new methods of synthesis of, for example, polyacrylamide, poly (alkyl cyanoacrylate PACA) and poly (isobutyl cyanoacrylate nanoparticles) which were used for entrapment of ampicillin.

Further studies on nanoparticles have shown that emulsions of these particles can be freeze-dried to remove water and reconstituted as needed without changing their properties or effect on particle size (11). Capacity and type of nanoparticle matrix that are used determine the efficiency of drug loading in the matrix

and subsequent drug release, thus overall loading ranging from 130 nm to 200 nm, without drug and with 2 mg/mL of ampicillin respectively. It was found that these nanoparticles enhance bioactivity of the  $\beta$ -lactam by 20 times in treating *L. monocytogenes* infection by diffused through the human cell to the target cell wall of the bacteria living inside. [12]

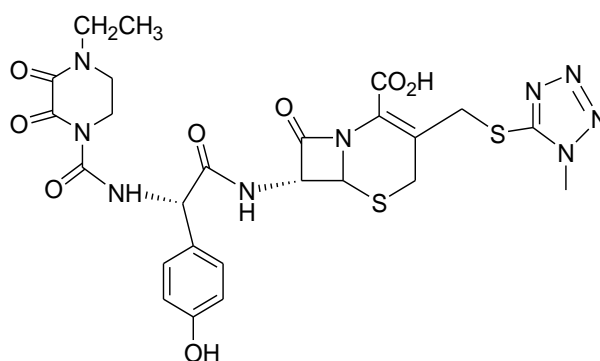
The author [12] has also reported metal nanoparticle for drug delivery. Simplicity to form a small size (5 nm) with regularity shape structure made these kind of drug carriers suitable for DNA, proteins, and antibiotics. During investigations it was found that silver nanoparticles are widely used as antimicrobial agents due to biocidal ability and non-toxicity to human cell. Silver nanoparticles with average size of 25 nm have strong antimicrobial and anti-bactericidal activities against both Gram-positive and Gram-negative bacteria, for instant methicillin-resistant *Aureus*. The antibacterial kinetics and minimum inhibitory concentration test showed that the silver/polymer (methyl methacrylate) nanofiber have three time killing rate than  $\text{AgNO}_3$  and nine-fold of silver sulfadiazine. In addition, this kind of polymer exhibited excellent activity against Gram positive bacteria (*S.aureus*) and Gram-negative bacteria (*Escherichia*

*coli*). At this stage, it was found that the combination of Nano silver with functional group of amoxicillin provides a promising alternative strategy to overcome antimicrobial resistance to the  $\beta$ -lactams Figure (12) [12]



**Figure (12): Combination of silver nanoparticles with number of reactive Functional groups of amoxicillin.**

The mechanism of this strategy depends on the Nano silver core which is surrounded by chelated amoxicillin molecules. In addition, it was also found that [12] cefoperazone a third-generation semisynthetic cephalosporin antibiotic is antibacterial agent against MRSA if used in conjunction with colloidal silver Figure (13).



**Figure (13): Cefoperazone**

Porous concave silica nanoparticles have been briefly investigated as drug delivery due to their extremely high chemical and thermal stability as well as a huge surface area for drug adsorption. These unusual nanoparticles are made by using calcium

carbonate as a template for the silica lattice to form an aqueous suspension. Evaporation the aqueous suspension produces spherical nanoparticles with diameter of 60-70 nm and the outer wall of the silica particle itself is about 10nm

thick. The cephalosporin, cefradine, has been used to plate the inside surface cleave of the porous silica particles. A new family of antibacterial compound exhibits promising activity against MRSA and  $\beta$ . *antbracis* within this family, N-alkylthio  $\beta$ -lactams has shown a new approach to form tackle the resistance problem by alternative mechanism of action.<sup>[12]</sup>

Although, the similarities structure to the penicillin and the monocyclic  $\beta$ -lactams such as the monobactams, however the acting manner were completely different, these compounds react rapidly with the bacterial cell with coenzyme A (COA) through the transfer of the N-thio group to alkyl-COA mixed disulfide species, which then interferes with fatty acid biosynthesis. As a result, N-alkylthio  $\beta$ -lactams Figure (14) show degradation and destruction of the cellular membranes instead of effecting bacterial morphology or cell wall structure. N-thiolate lactams have been used against MRSA and  $\beta$ . *antbracis* after incorporated into polyacrylate styrene nanoparticles by radical-induced emulsion polymerization<sup>[12]</sup>

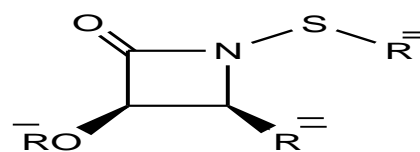


Figure (14): Structure of N-alkylthio  $\beta$ -lactams

In 2012, Alekseev<sup>[5]</sup> published a review including the interaction of penicillin and cephalosporin antibiotic with metals as the key step to influence the antimicrobial activity, resistance to hydrolysis, toxicity and pharmacokinetics Figure (15).

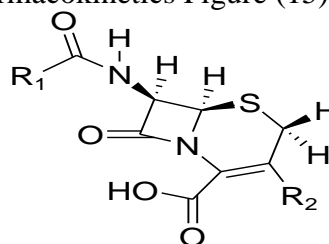


Figure (15): cephalosporin

Improvements in the properties of penicillin and cephalosporin were achieved by altering the structures of side chains-radicals R for penicillin and R<sup>1</sup>, R<sup>2</sup> for cephalosporin Tables (1) and (2)<sup>[5]</sup>

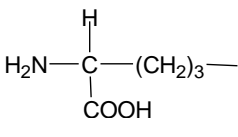
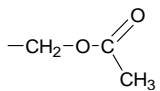
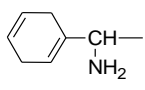

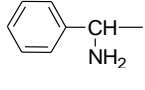

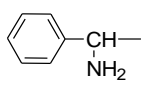

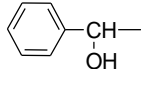
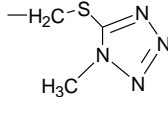
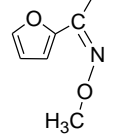
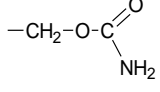
Table (1) penicillin 1,2,4

Name	Radical structure
<b>Benzl-penicillin</b> <b>(Penicillin G), I</b>	
<b>Para-hydroxyl benzyl penicillin</b> <b>(penicillin X), II</b>	
<b>Pentylene penicillin</b> <b>(penicillin F), III</b>	CH <sub>3</sub> -CH <sub>2</sub> -CH=CH-CH <sub>2</sub> -
<b>Heptyl penicillin</b> <b>(penicillin K), IV</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> -

In 2014, Masoud *and etal* [16] published a review of classification of beta lactam, activity, clinical uses, pharmacokinetics, and various analytical methods for the analysis of antibiotics. Authors have classified the antibiotic cephalosporins into five generations according to the chemical structure and the activity against several types of bacteria Table (2) [5]. HPLC methods, thin layer chromatographic,

visible, spectroph- optometric, and atomic absorption spectrometric methods have been used for determination of the antibiotic. Moreover, this review shows the modification of penicillin and their family by synthetic and semisynthetic routes in order to extend their range of activity for instant the addition of beta lactamase inhibitors to some aminopenicillins [16].

**Table (2): Cephalosporins 1-6**

Name	R <sup>1</sup>	R <sup>2</sup>	Other name
Cephalosporin C, XIV			
Cephradine XV			First generation ref. <sup>16</sup> Velosef®
Cephalexin, XVI			
Cefaclor, XVII			Second generation ref. <sup>16</sup> Ceclor®
Cefamandole, XXIV			Second generation ref. <sup>16</sup> Mandol®
Cefuroxime, XXVI			Second generation ref. <sup>16</sup> Axetil (Ceftin)®

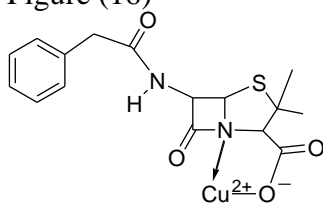
The old study addressing metal complexes of penicillin was depended on the interaction of potassium salt of benzylpenicillin (Bzp) and  $\text{Cu}^{2+}$  ion in

aqueous solution by ion exchange <sup>(5)</sup> Complexes of CuBzp and Cu ( $\pi$ ) were identified and some of their formation constants were determined in **Table (3)**.

**Table (3): Some examples of formation constants of metal complexes of penicillin and cephalosporin (5)**

Antibiotic	complex	lg $\beta$	Conditions of identification
Benzylpenicillin	$\text{CuL}^+$	4.8	25°C, ion exchange
	$\text{CuL}_2$	7.1	
	$\text{CuL}^+$	2.61±0.01	30 °C, $I=0.01$
	$\text{CuL}^+$	2.65	37 °C, spectrophotometry
	$\text{NiL}^+$	1.74	25 °C, 0.15 M $\text{NaClO}_4$ , potentiometry
Methicillin Phenoxymethyl- penicillin	$\text{CuL}^+$	2.91	37 °C, spectrophotometry
	$\text{CuL}^+$	2.09±0.09	30 °C, $I=0.01$
	$\text{AgL}$	4.8	20 °C, $I=0.1$
	$\text{PbL}^+$	4.9	
	$\text{znL}^+$	4.9	
	$\text{CuL}^+$	5.91	20 °C, methanol, spectrophotometry
	$\text{CuL}_2$	10.62	
	$\text{CoL}^+$	1.67	20 °C, methanol, spectrophotometry
	$\text{CoL}_2$	5.76	
cloxacillin	$\text{ZnL}^+$	5.44	
carbenicillin	$\text{CuL}$	3.07	20 °C, 0.1M $\text{KNO}_3$
cephaloridine	$\text{CaL}^+$	3.75	25 °C, 0.1 M $\text{KNO}_3$ , potentiometry
Amoxicillin	$\text{CuHL}^+$	15.51±0.03	25 °C, 0.1 M $\text{NaNO}_3$ , potentiometry
	$\text{NiHL}^+$	13.01±0.06	
	$\text{CO}(-\text{H})\text{L}^-$	-3.47±0.07	
	$\text{ZnHL}^+$	12.12±0.06	
Cephalexin	$\text{AgL}$	3.72±0.03	20 °C , 0.2 M $\text{KNO}_3$ , potentiometry
	$\text{AgL}_2^-$	7.36±0.04	
	$\text{MnL}^+$	0.75±0.06	

It was found that these complexes have chelates properties because of coordination of the ligand the benzylpenicillin anion ( $\text{Bzp}^-$ ) via oxygen atom of the carboxylate group and N atom of the beta-lactam group Figure (16) <sup>[5]</sup>.



**Figure (16) Complex 1**

Studies reported on Cu ( $\pi$ ) complexes showed that catalyst amount of  $\text{Cu}^{+2}$  ion can hydrolysis of penicillin to penicilloic at pH 4-6. In addition, the effects of  $\text{Cu}^{+2}$  irons and their complexes on the kinetic of  $\text{Bzp}^-$ , phenoxymethylpenicillin ( $\text{Fmp}^-$ ), and methicillin ( $\text{Met}^-$ ) hydrolysis were also investigated. The constants of formation of Cu ( $\pi$ ) complexes with  $\text{Bzp}^-$  and  $\text{Met}^-$  were determined and were in good agreement with the result obtained from previous studies, which also show at that

the values of  $lg \beta(\text{CuL})$  were high. On the other hand, Djoko *etal* <sup>[17]</sup> have demonstrated the effected of copper coordination complexes as adjuvant in clinical therapeutics to inhibit the activity of NDM-1 gene which is change the characteristics of bacteria and makes them resistant to Carbapenem  $\beta$ -lactam antibiotics.

From the NMR studies the complexed  $\text{CuBzp}^+$  has the structure of Complex (1).  $\text{Cu}(\text{II})$  catalytic influence on the hydrolysis of  $\text{Bzp}^-$  by 1000-10000 time than that of  $\text{Zn}(\text{II})$ ,  $\text{Ni}(\text{II})$ , and  $\text{Co}(\text{II})$ . At pH 6-7 interaction of  $\text{NaBzp}$  with  $\text{Cu}(\text{CH}_3\text{COO})_2$  furnished  $[\text{Cu}_2\text{Bzp}]^{3+}$  complex which was green in color with  $\lambda_{\text{max}} = (650\text{nm})$  and persisted for 25 min. Spectrophotometric studies of  $\text{Fmp}^-$  with  $\text{Cu}(\text{II})$  and  $\text{Co}(\text{II})$  demonstrated formation of complexes  $\text{ML}$  and  $\text{ML}_2$  analogous to Complex (1) via coordination of  $\text{Fmp}^-$  carboxylate group and the beta-lactam N atom. <sup>[5]</sup>

Computer modeling of the structure of the complex of  $\text{Zn}(\text{II})$  with anion of hypothetical methylpenicillin in aqueous solution using the AM1 and PM3 semiempirical method predicted two possible variants of ligand coordination

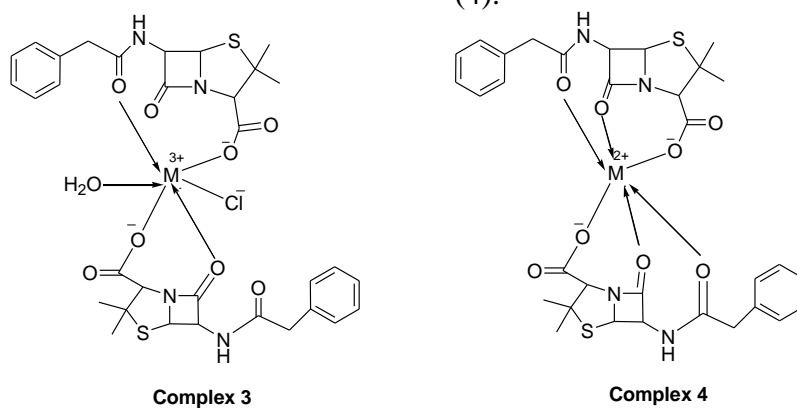


Figure (18): Complex 3 and 4

Solid complexes of  $\text{Bzp}^-$  with  $\text{Fe}(\text{II})$  were investigated by IR spectroscopy. The results obtained have shown that  $\text{Bzp}^-$  is coordinated via the carboxylate group and the beta-lactam N atom (analogous to complex 1). Complexes (5), and (6), were prepared by interaction of methanolic suspension of  $\text{NaBzp}$  and methanolic

first, coordination analogous to coordination in complex (1) or via the two oxygen atoms of carboxylate group. <sup>[5]</sup> (Figure 17).

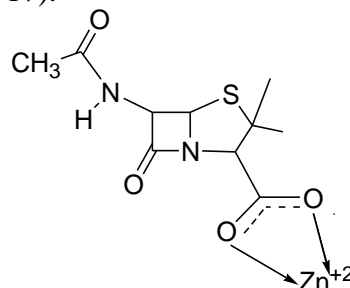
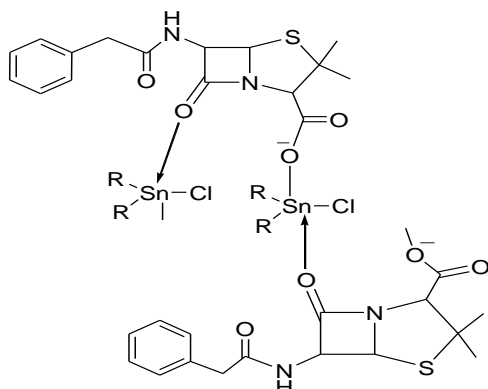


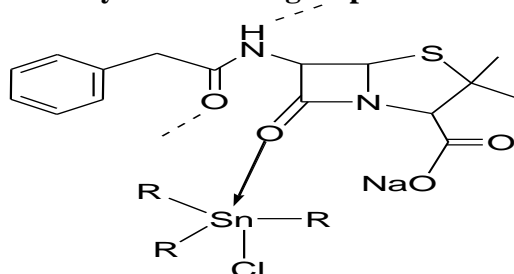
Figure (17): Complex 2 more favored energetically

Solution of complexes of  $\text{Bzp}^-$  with  $\text{Ni}(\text{II})$ ,  $\text{Zn}(\text{II})$ ,  $\text{Cd}(\text{II})$ ,  $\text{Fe}(\text{III})$ , and  $\text{La}(\text{III})$  in DMSO were studied by UV/visible spectrophotometry, elemental analysis along with IR and EPR spectroscopy. The results obtained led to the conclusion that in  $\text{Fe}(\text{III})$  and  $\text{La}(\text{III})$  complexes, the ligands were coordinated via oxygen atoms of the carboxylate and amide groups Complex (3) while coordination's in  $\text{Ni}(\text{II})$ ,  $\text{Zn}(\text{II})$ , and  $\text{Cd}(\text{II})$  complexes also involve the O atoms of the beta lactam group <sup>[5]</sup> <sup>[18]</sup> Complex (4).

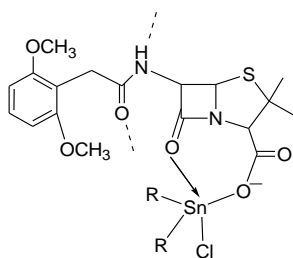
solutions of  $\text{R}_2\text{SnCl}_2$  and  $\text{R}_3\text{SnCl}$  ( $\text{R}=\text{Me}$ ,  $\text{Bu}$ ,  $\text{ph}$ ) in equimolar ratios. <sup>[5]</sup>



**Figure (19): Complex 5  $R_2SnClBzp$  had polymeric structure with  $Bzp^-$  as Bidentate bridging ligand coordinated via the beta-lactam O atom and the carboxylate atom O group**



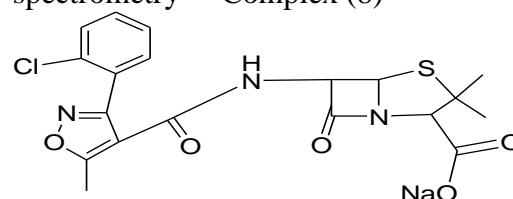
**Figure (20): Complex 6  $R_3SnClBzpNa$  had monomeric structure but linked to each other via amide group hydrogen bonds.**



**Figure (21): Complex 7  $R_2SnClMet.H_2O$  showed coordination of the ligand via the carboxylate and beta-lactam O atoms with formation of a chelate ring, however polymeric of  $Bzp^-$  complex was not proved.**

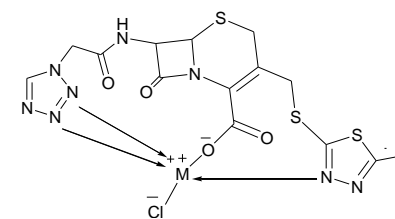
Interaction of Zn (II) and Co (II) complexes with the anionic cloxacillin ( $Cxc^-$ ) in solid form and in DMSO solution was described by IR spectroscopic along with computer modeling of the structure of these compounds by the PM<sub>3</sub> method. The results showed that there was no

coordination between complex-forming ions with the beta lactam carbonyl O atom. In different study interaction of Zn (II) and NaCxc in aqueous solution was study by UV spectroscopy and fluorescence analysis, which showed that mono ligand complex was formed, and its formation constant was measured. The product of interaction was obtained in solid form and studied by IR spectroscopy, differential scanning calorimetry and NMR spectrometry [5] Complex (8)

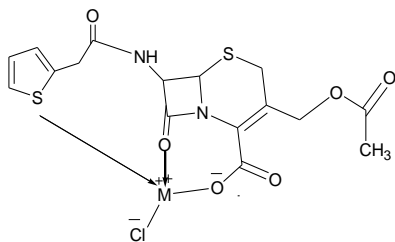


**Figure (22): Complex 8  $Cxc^-$  is coordinated with a Zn+2 ion via the oxygen atoms of the amide and beta-lactam groups.**

Complexes of composition  $MLCl$  were obtained as precipitates by interaction of metal chlorides with NaCzl or NzClt in methanol at molar ratio of 1:2. Solid complexes were studied by elemental analysis, IR spectroscopy, PMP, and EPR, Complex (9) [5]

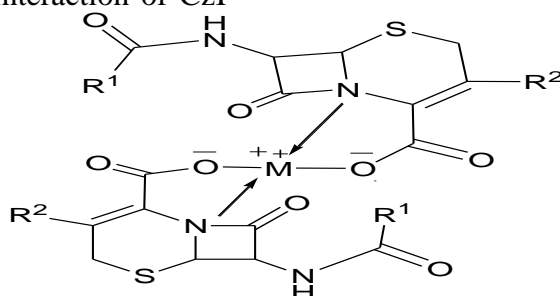


**Figure (23): Complex 9 Cefazolin  $Czl^-$  coordinated via the carboxylate and Amide O atom and the N atom of the heterocyclic side chain. Coplex were insoluble water and methanol, and well soluble in DMF and DMSO.**



**Figure (24): Complex 10 Pd (II) also coordinated with  $\text{CzI}^-$  via the oxygen atom of Beta-lactam and with  $\text{Cl}^-$  via the carboxylate group and oxygen atom of beta-lactam group and the S atom of the heterocyclic side chain.**

According to author <sup>(5)</sup>, in 2003, other researcher reported the interaction of  $\text{CzI}^-$

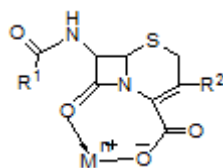


**Figure (25): Complex 11: was studied by elemental analysis, IR spectroscopy, and thermic analysis. These data led to inference that antibiotic anion was coordinated via the O atom of the carboxylate group and the beta-lactam group N atom. This complex was soluble in DMF, and DMSO and insoluble in water, ethanol, acetone and ether.**

Interaction of the same sort of antibiotic with  $\text{Cu}^{2+}$ ,  $\text{Cd}^{2+}$  and  $\text{Zn}^{2+}$  ions in aqueous solution at  $26^\circ\text{C}$  and pH 7.34 were studied by cyclic voltammetry and complexes of composition  $\text{ML}_2$  were also observed. Alekseev <sup>(4)</sup>, also described the conditions that were used for formation of complex of  $\text{Ca}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Pb}^{2+}$  and  $\text{La}^{3+}$  with cephaloridine and cefoperazone <sup>[5]</sup> Table (3).

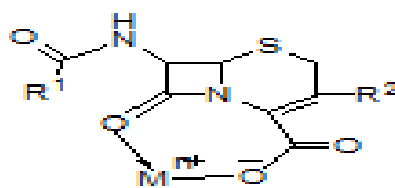
In summary, reported data led to the conclusion that penicillin's and cephalosporins of the acid type generally show quite weak ligand properties. Their

anions were able to form complexes with low and intermediate stability with cationic p and d block elements for instance, complexes with significant proportion of covalent bonds. In all the studied complexes, the ligand coordination via was the carboxylate group and the beta-lactam group and this has led to the conclusion that the coordination of the beta-lactam group depended on the chemical nature of the complex ion formation. This means that the oxygen atom was involved in the coordination <sup>[5]</sup> Structure (1).



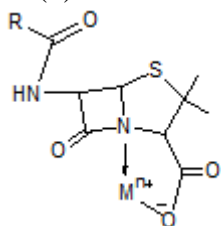
**Structure(1)(A) Penicillines**





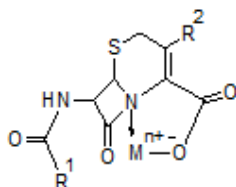
Structuer(1)(B) cephalosporins

In some cases, coordination of Hg ( $\pi$ ), and Cu ( $\pi$ ) metal with the N atom leads to weakening of the C-N bond and subsequently cleavage of the beta-lactam ring Structure (2) <sup>[5]</sup>

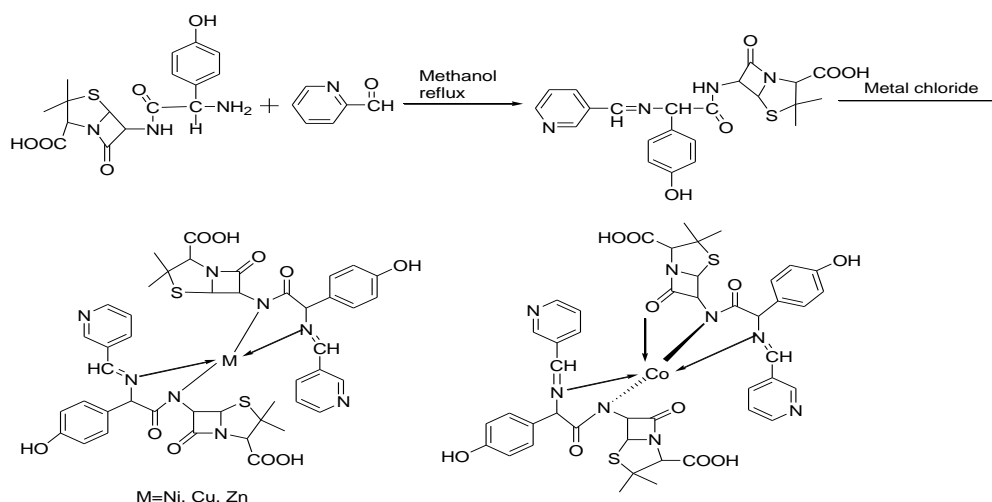


Structure(2)(A) Penicillines

For cephalosporins, side chains can be involved in the coordination of heterocycles, as a result increasing the stability of such complexes <sup>[5]</sup> Structure (2 b).



Structure(2)(B) cephalosporins



Schem (2): Preparation of Schiff base and its metal complexes

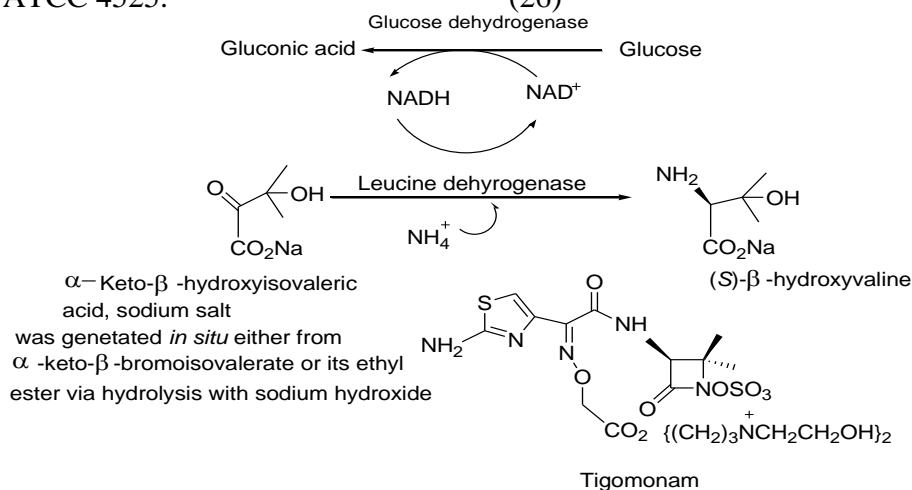
Metal complexes of amphoteric antibiotics with carboxyl and amide groups will be discuss in the next review.

One of the more recently type of antibiotic resistance is that caused by synthesis of Schiff base ligand, by the condensation of amoxicillin trihydrate and crotonaldehyde and its four metal complexes with cobalt(II), nickel(II), copper(II), and zinc(II) salts Scheme (2). The coordination behavior of the ligand towards transition metal ions was fully characterized by various spectroscopy and thermal techniques. Evaluated the antibacterial efficacy of ligand and its metal complexes against *S. aureus*, *E. coli*, *K. pneumoniae*, and *P. vulgaris* bacteria have also investigated.

Complexes of Co, Zn, Ni, and Cu wear shown highly active against all the bacterial pathogens at their higher concentration; except the copper complex has shown less active than others. <sup>[19]</sup>

In 2013, Patel <sup>[20]</sup> reported study toward the total synthesis of orally active monobactam Tigemonam. The route required synthesis chiral amino acid (S)- $\beta$ -hydroxyvaline as the key step to form the target compound. The synthetic method was used including reductive amination of  $\alpha$ -keto- $\beta$ -hydroxy isovalerate under enzyme catalyzes leuDH from *Bacillus sphaericus* ATCC 4525.

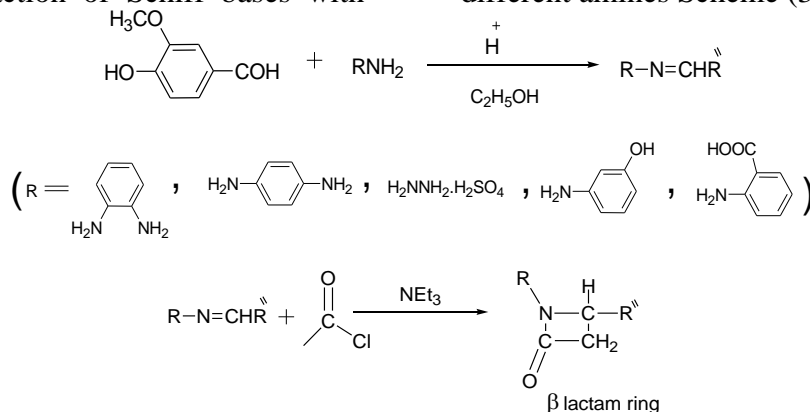
Nicotinamideadenine dinucleotide(NADH) required for this kind of reaction and was regenerated by either formate dehydrogenase from *Candida boidinii* or glucose dehydrogenase from *Bacillus megaterium*. The Tigemonam in this process was obtained in yield of 89% and an enantiomeric excess of 99.8% were obtained from the L- $\beta$ -hydroxyvaline Figure (26)



**Figure (26): Tigemonam; Enzymatic synthesis of (S)- $\beta$ -hydroxyvaline**

In the same year, Sadoon <sup>[21]</sup> published synthesis of cyclic compounds containing one or two of beta lactam ring by Staudinger reaction of Schiff bases with

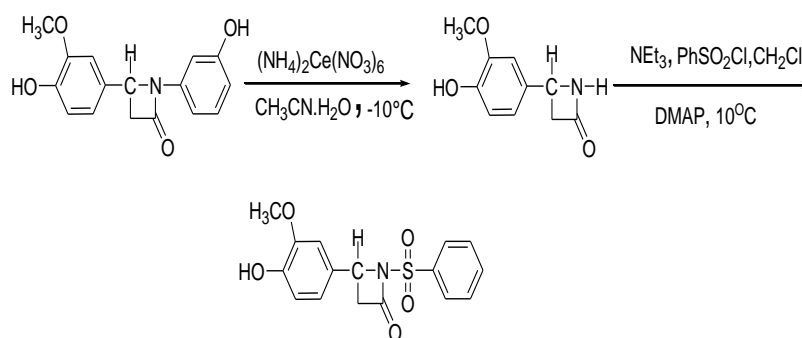
acetyl chloride in the presence of triethyl amine as a base. The Schiff bases were prepared by reaction of vanillin with different amines Scheme (3).



**Schem (3): Prepration of Schiff base and beta lactam respectively**

In addition, the author has converted one of the beta lactam compounds to N sulfonyl beta-lactam in the presence of sulfonyl chloride and catalytic quantities of dimethylamino pyridine Scheme (4). The

structure of the Schiff bases and beta-lactam compounds were characterized by elemental analysis, IR and NMR spectroscopy <sup>[21]</sup>



Scheme (4): Synthesis of N sulfonyl beta-lacta

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