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CHEMISTRY OF β-LACTAM SULTAMICILLIN AS A MUTUAL PRODRUG OF AMPICILLIN AND SULBACTAM WORKS AS AN AZABICYCLO[3.2.0]HEPTANE CARBOPENAM BIOPRECURSOR

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ABSTRACT

A large number of therapeutic medications have undesirable properties that may generate pharmacological, pharmaceutical, or pharmacokinetic barriers in clinical drug applications. Metabolism of drugs by Phase-I & Phase-II metabolic pathways for possibility of active metabolites, which could in turn useful for rational designing of bioprecursor prodrugs of the active principle of interest. Prodrug is a substance which after administration is metabolized into a pharmacologically active drug. Actually Prodrug has least medicinal value in in-vitro/in-vivo but after biotransformation by metabolism in in-vivo it releases the active medicament. A drug is a substance which is a chemical entity, has definite structural skeleton, obtained by natural or synthetic or semisynthetic source, which can fit on bioreceptor platform having controlling capacity to control over the biochemical malfunction. Every drug is xenobiotic because it is coming from outer source (xeno) and active in biological unit (biotic). Prodrug is the precursor of drug which is made by derivatization of the same to enhance the bioavailability by pharmacokinetics, lipid solubility by partition coefficient and increase the physicochemical & biochemical parameters by pharmacodynamics. Prodrug is a precursor (forerunner) of a drug. A prodrug must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent. For example, sultamicillin is a prodrug. It is not active in its ingested form. It has to be broken down before becoming active as a drug. It is a compound that on administration undergoes chemical conversion by metabolic processes to yield active moieties of ampicillin and sulbactam. This is also is called as biotransformation which produces active drug for pharmacological response from prodrug which is inactive by itself.

KEYWORDS: Mutual pro-drug, Sulbactam, Ampicillin, Sultamicillin, Pro-drug, Biotransformation, ADME, Xenobiotic, Receptor, Pharmacodynamics, Pharmacokinetics.

INTRODUCTION

A **prodrug** is a medication or compound that, after administration, is metabolized (i.e., converted within the body) into a pharmacologically active drug. **Inactive prodrugs** are pharmacologically inactive medications that are metabolized into an active form within the body. Instead of administering a drug directly, a corresponding prodrug might be used instead to improve how a medicine is absorbed, distributed, metabolized and excreted (ADME). Prodrugs are often designed to improve bioavailability when a drug itself is poorly absorbed from the GIT. A prodrug may be used to improve how selectively the drug interacts with cells or processes that are not its intended target. This reduces adverse or unintended effects of a drug, especially important in treatments like chemotherapy, which can have severe unintended and undesirable side effects.[1-3]

There are three basic, overlapping objectives in prodrug research:

1. Pharmaceutical Objectives: To improve solubility, chemical stability and organoleptic properties. To decrease irritation and/or pain after local administration. To reduce problems related with the pharmaceutical technology of the active agent. To improve absorption (oral and by non-oral routes). To decrease presystemic metabolism to improve time profile. To increase organ/tissue-selective delivery of the active agent.
2. Pharmacokinetic Objectives: To improve absorption (oral and by non-oral routes). To decrease presystemic metabolism to improve time profile. To increase organ/tissue-selective delivery of the active agent.
3. Pharmacodynamic Objectives: To decrease toxicity and improve therapeutic index. To design single chemical entities combining two drugs (co-drugs strategy).

Prodrug concept: The awareness that the onset, intensity and duration of drug action are greatly affected by the physicochemical properties of drug has promoted the emergence of various prodrugs. Most of the limitations can be overcome by prodrug approach, but after overcoming the various barriers, the prodrug should rapidly convert into active moiety after reaching the target site. The design of an efficient, stable, safe, acceptable and aesthetic way to target a drug to its site of action while overcoming various physical, chemical and social barriers is certainly the utilization of the prodrug approach holds great potential.[4]

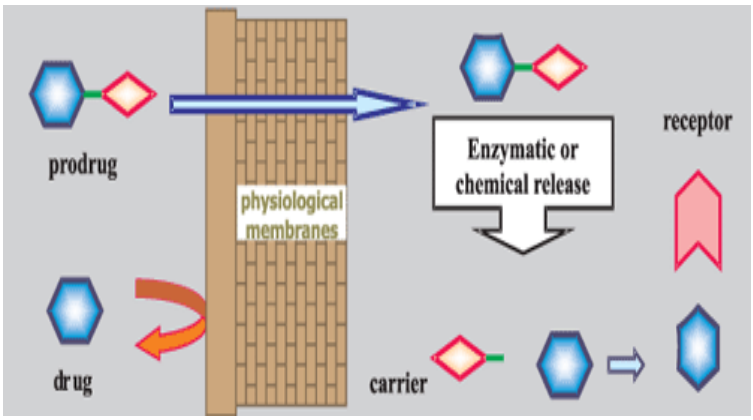

Figure-1: Prodrug approach.

Carrier linked prodrug: Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties. The subsequent enzymatic or non-enzymatic mechanism releases the active drug moiety. Active Drug→Inert Carrier→Inert carrier+Drug Chemical→Prodrug Formation→Chemical/Enzymatic cleavage *in-vivo* Covalent Bond.

Bipartite prodrug: It is composed of one carrier (group) attached to the drugs. Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically e.g. Tolmetin-glycine prodrug.

Tripartite prodrug: The carrier group is attached via linker/spacer to drug.

Mutual Prodrugs: A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa. A mutual prodrug is a bipartite or tripartite prodrug in which the carrier is a synergistic drug with the drug to which it is linked. Benorylate is a mutual prodrug of aspirin and paracetamol. **Sultamicillin, which on hydrolysis by an esterase produces ampicillin & sulbactum**. Aspirin+Paracetamol produce Benorylate, **Sulbactum+Ampicillin produce Sultamicillin**.[5]

Bioprecursors: The bioprecursor does not contain a temporary linkage between the active drug and carrier moiety, but designed from a molecular modification of an active principle itself. e.g.: phenylbutazone. Phenylbutazone gets metabolized to oxyphenbutazone that is responsible for the antiinflammatory activity of the parent drug. Polymeric Prodrugs: Also known as macromolecular prodrug, the drug is dispersed or incorporated into the polymer (both naturally occurring and synthetically prepared) system without formation of covalent bond between drug and polymer. e.g.: p–phenylene diamine mustard is covalently attached to polyamino polymer backbone polyglutamic acid.

Chemistry
Sulbactam (CAS Number: 68373-14-8)

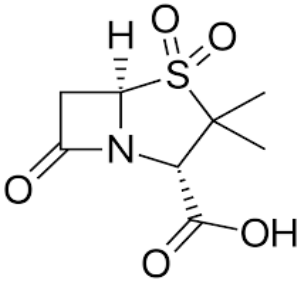

Figure-2: Sulbactam.

(2S,5R)-3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide

It has two chiral points 2S (-COOH is attached) & 5R (-H is attached). It is an azabicyclo[3.2.0]heptane penam ring. It has molecular weight=233.243g/mol, molecular formula=$C_8H_{11}NO_5S$, logP=-0.92, pKa=3.09 (acidic property generates from free carboxylic acid [-COOH]), water solubility=48.5mg/mL, melting point=170°C. It is highly polar so it's water solubility is 48.6mg/mL and logP is -0.92.[6]

Sulbactam is a β-lactamase inhibitor. This drug is given in combination with β-lactam antibiotics to inhibit β-lactamase, an enzyme produced by bacteria that destroys the antibiotics. Sulbactam is an irreversible inhibitor of β-lactamase; it binds to the enzyme and does not allow it to degrade the antibiotic. Sulbactam is able to inhibit the most common forms of β-lactamase but is not able to interact with the AmpC Cephalosporinase. Thus, it confers little protection against bacteria such as *Pseudomonas aeruginosa*, *Citrobacter*, *Enterobacter* and *Serratia*, which often express this gene.

Enterobacter is a genus of common Gram-negative, facultatively anaerobic, rod-shaped, non-spore-forming bacteria of the family Enterobacteriaceae. Several strains of these bacteria are pathogenic and cause opportunistic infections in immunocompromised (usually hospitalized) hosts and in those who are on mechanical ventilation. The urinary and respiratory tracts are the most common sites of infection. The genus *Enterobacter* is a member of the coliform group of bacteria. It does not belong to the fecal coliforms (or thermotolerant coliforms) group of bacteria, unlike *Escherichia coli*, because it is incapable of growth at 44.5°C in the presence of bile salts. Some of them showed quorum sensing properties as reported before. Two clinically important species from this genus are *E.aerogenes* and *E.cloacae*. The genus *Enterobacter* ferments lactose with gas production during a 48-hour incubation at 35-37°C in the presence of bile salts and detergents. It is oxidase-negative, indole-negative and urease-variable.[7]

Citrobacter is a genus of Gram-negative coliform bacteria in the Enterobacteriaceae family. The species *C.amalonaticus*, *C.koseri* and *C.freundii* can use citrate as a sole carbon source. *Citrobacter* species are differentiated by their ability to convert tryptophan to indole (*C.koseri* is the only citrobacter to be commonly indole-positive), ferment lactose (*C.koseri* is a non-lactose fermentor) and use malonate. *Citrobacter* shows the ability to accumulate uranium by building phosphate complexes.

Serratia is a genus of Gram-negative, facultatively anaerobic, rod-shaped bacteria of the Enterobacteriaceae family. The most common and pathogenic of the species in the genus, *S.marcescens*, is normally the only pathogen and usually causes nosocomial infections. However, rare strains of *S.plymuthica*, *S.liquefaciens*, *S.rubidaea* and *S.odoriferae* have caused diseases through infection. *S.marcescens* is typically found in showers, toilet bowls and around wetted tiles. Members of this genus produce characteristic red pigment, prodigiosin and can be distinguished from other members of the Enterobacteriaceae family by their unique production of three enzymes: DNase, lipase and gelatinase. A pan-genome analysis of the genus *Serratia* revealed that it does not depict exceptional genetic conservation or diversity as compared to other bacterial genera.[8,9]

Ampicillin (CAS Number: 69-53-4)

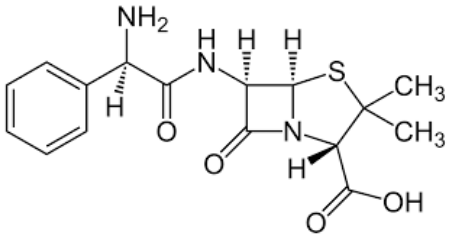

Figure-3: Ampicillin.

(2S,5R,6R)-6-([(2R)-2-amino-2-phenylacetyl]amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. Ampicillin is an antibiotic used to prevent and treat a number of bacterial infections, such as respiratory tract infections, urinary tract infections, meningitis, salmonellosis, and endocarditis. It may also be used to prevent group B streptococcal infection in newborns. It is used by mouth, by injection into a muscle, or intravenously. Like all antibiotics, it is not useful for the treatment of viral infections.

It has three chiral points 2S (-COOH is attached), 5R (-H is attached), 6R (-H is attached). It is an azabicyclo[3.2.0]heptane penam ring. It has molecular weight=349.405gm/mol, molecular formula=$C_{16}H_{19}N_3O_4S$, logP=1.35, pKa=3.24 (acidic property generates from free carboxylic acid group [-COOH]) & 7.44 (basic property generates from primary amino nitrogen of chain and tertiary amino nitrogen atom of the ring), water solubility=0.605mg/mL, melting point=208°C. It is semipolar so it's water solubility is 0.605mg/mL and logP is 1.35.

Common side effects include rash, nausea, and diarrhea. It should not be used in people who are allergic to penicillin. Serious side effects may include *Clostridium difficile* colitis or anaphylaxis. While usable in those with kidney problems, the dose may need to be decreased. Its

use during pregnancy and breastfeeding appears to be generally safe.

Ampicillin is in the penicillin group of β-lactam antibiotics and is part of the aminopenicillin family. It is roughly equivalent to amoxicillin in terms of activity. Ampicillin is able to penetrate Gram-positive and some Gram-negative bacteria. It differs from penicillin G, or benzylpenicillin, only by the presence of an amino group. That amino group helps the drug penetrate the outer membrane of Gram-negative bacteria. Ampicillin acts as an irreversible inhibitor of the enzyme transpeptidase, which is needed by bacteria to make the cell wall. It inhibits the third and final stage of bacterial cell wall synthesis in binary fission, which ultimately leads to cell lysis; therefore, ampicillin is usually bacteriolytic.[10-12]

Ampicillin has been used extensively to treat bacterial infections since 1961. Until the introduction of ampicillin by the British company Beecham, penicillin therapies had only been effective against Gram-positive organisms such as *staphylococci* and *streptococci*. Ampicillin (originally branded as 'Penbritin') also demonstrated activity against Gram-negative organisms such as *H.influenzae*, *coliforms* and *Proteus* spp. Ampicillin is used to treat infections by many Gram-positive and Gram-negative bacteria. Ampicillin was the first 'broad spectrum' penicillin with activity against Gram-positive bacteria including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, some isolates of *Staphylococcus aureus* (but not penicillin-resistant or methicillin-resistant strains) and some *Enterococcus*. Activity against Gram-negative bacteria includes *Neisseria meningitidis*, some *Haemophilus influenzae* and some of the Enterobacteriaceae. Its spectrum of activity is enhanced by co-administration of **sulbactam**, a drug that inhibits β-lactamase, an enzyme produced by bacteria to inactivate ampicillin and related antibiotics. It is sometimes used in combination with other antibiotics that have different mechanisms of action, like vancomycin, linezolid, daptomycin and tigecycline. Ampicillin can be administered by mouth, an intramuscular injection (shot) or by intravenous infusion.[13-15]

Ampicillin/sulbactam is a combination of the common penicillin-derived antibiotic ampicillin and sulbactam, an inhibitor of bacterial β-lactamase. Two different forms of the drug exist. The first, developed in 1987 and marketed in the United States under the tradename Unasyn, generic only outside of the United States, is an intravenous antibiotic. The second, an oral form called sultamicillin, is marketed under the trade name Ampictam outside of the United States. And generic only in the United States, ampicillin/sulbactam is used to treat infections caused by bacteria resistant to β-lactam antibiotics. Sulbactam blocks the enzyme which breaks down ampicillin and thereby allows ampicillin to attack and kill the bacteria. Ampicillin sodium is derived from the basic penicillin nucleus, 6-aminopenicillanic acid. Its chemical name is monosodium (2S,5R,6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. It has a molecular weight of 371.39grams and its chemical formula is $C_{16}H_{18}N_3NaO_4S$. Sulbactam sodium is also a derivative of 6-aminopenicillanic acid. Chemically, it is known as either sodium penicillinate sulfone or sodium (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide. It has a molecular weight of 255.22grams and its chemical formula is $C_8H_{10}NNaO_5S$. Ampicillin/sulbactam is also used when the cause of an infection is not known (empiric therapy), such as intra-abdominal infections, skin infections, pneumonia and gynecologic infections. It is active against a wide range of bacterial groups, including *Staphylococcus aureus*, *Enterobacteriaceae* and anaerobic bacteria. Importantly, it is not active against *Pseudomonas aeruginosa* and should not be used alone when infection with this organism is suspected or known. Ampicillin/sulbactam is a combination of a β-lactam antibiotic and a β-lactamase inhibitor. Ampicillin works by binding to penicillin-binding proteins (PBPs) to inhibit bacterial cell wall synthesis. This causes disruption of the bacterial cell wall and leads to bacterial cell death. However, resistant pathogens may produce β-lactamase enzymes that can inactivate ampicillin through hydrolysis. This is prevented by the addition of sulbactam, which binds and inhibits the β-lactamase enzymes. It is also capable of binding to the PBP of *Bacteroides fragilis* and *Acinetobacter* spp., even when it is given alone. The activity of sulbactam against *Acinetobacter* spp. seen in *in-vitro* studies makes it distinctive compared to other β-lactamase inhibitors, such as tazobactam and clavulanic acid.

The introduction and use of ampicillin alone started in 1961. The development and introduction of this drug allowed the use of targeted therapies against gram-negative bacteria. With the rise of β-lactamase producing bacteria, ampicillin and the other penicillin-derivatives became ineffective to these resistant organisms. With the introduction of β-lactamase inhibitors such as sulbactam, combined with ampicillin made β-lactamase producing bacteria susceptible.

Sultamicillin (CAS Registry Number: 76497-13-7)

Sultamicillin is an oral form of the antibiotic combination (codrug or mutual prodrug) ampicillin/sulbactam. It contains esterified ampicillin and sulbactam and is marketed under a number of trade names, e. g. Unasyn from Pfizer. The drug is also marketed by many Indian companies as 375 mg tablets for oral use. The pharmacokinetic properties of sultamicillin are improved compared to a combination of ampicillin and sulbactam. Sultamicillin increases the absorption and decreases the chances of diarrhea and dysentery. The inclusion of sulbactam extends ampicillin's spectrum of action to β-lactamase producing strains of bacteria. Oral sulbactam form provides a regimen of continuous sulbactam therapy throughout the treatment, resulting in better clinical results.

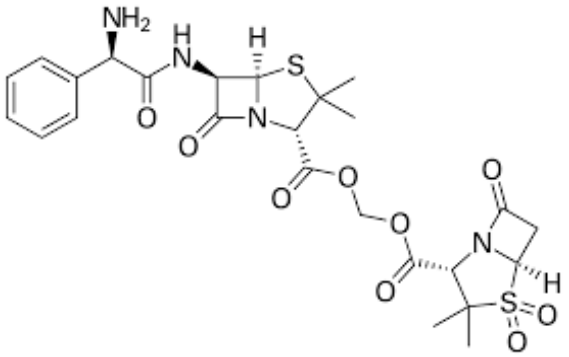

Figure-4: Sultamicillin.

[(2R)-3,3-Dimethyl-4,4,7-trioxy-4λ6-thia-1-azabicyclo[3.2.0]heptane-2-carbonyl]oxymethyl(2R)-6-{[(2S)-2-amino-2-phenyl-acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate. It is an azabicyclo[3.2.0]heptane penam ring. It has six chiral points out of that 2R is common in which ampicillin unit and sulbactam units are joined by ester linkages with methylene diol, amino part of ampicillin is connected by 2S linkage, 6th position of ampicillin is connected with imino nitrogen of thia-1-azabicyclo[3.2.0]heptane, so it is 4λ6-thia. It has molecular weight=594.659g/mol, molecular formula=$C_{25}H_{30}N_4O_9S_2$, logP=1.55, pKa=11.71 (acidic property generates from keto-enol tautomerism of amide linkage [-CONH-] of the chain & 7.23 (basic property generates from primary amino of chain and tertiary nitrogen atoms of the two rings), water solubility=0.283mg/mL, melting point=190°C. It is highly nonpolar so it's water solubility is 0.283mg/mL and logP is 1.55.

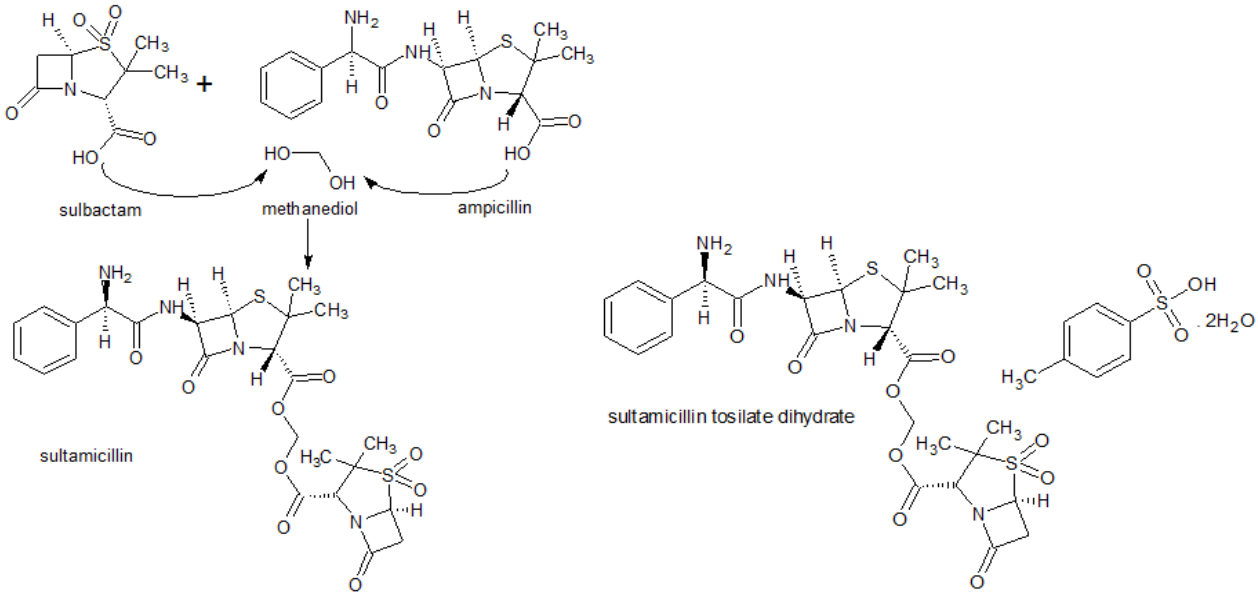

Figure-5: Sultamicillin prodrug and Sultamicillin Tosilate salt.

Sultamicillin and Sultamicillin Tosilate both are official drug in European Pharmacopoeia.[16] Sultamicillin [$C_{25}H_{30}N_4O_9S_2$] is a mutual prodrug of sulbactam and ampicillin attached with methane diol whereas Sultamicillin Tosilate [$C_{32}H_{38}N_4O_{12}S_3$] is a salt of sultamicillin and toluene sulphonic acid. Sultamicillin hydrolyses into sulbactam and ampicillin by cleavage of ester linkage and Sultamicillin Tosilate releases toluene sulfonic acid first as it makes salt with free amino group (-NH_2) with sulphonic acid (-SO_3H) part and after that free sultamicillin releases the sulbactam and ampicillin by cleavage of ester linkage made by covalent bond by hydrolysis. Sultamicillin is a prodrug of ampicillin and β-lactamase inhibitor sulbactam, it consists of two compounds linked as a double ester. During absorption from gastrointestinal tract it is hydrolyzed, releasing equimolar quantities of sulbactam and ampicillin. Sultamicillin is given orally as tablets containing sultamicillin tosilate or as oral suspension containing sultamicillin. It is used in the treatment of infections where β-lactamase producing organisms might occur, including uncomplicated gonorrhea, otitis media, respiratory tract and urinary tract infections. The usual dose is 375-750mg of sultamicillin equivalent to 147-294mg of sulbactam and 220-440mg of ampicillin.

Sultamicillin tosilate salt of the double ester of sulbactam plus ampicillin. Sulbactam is a semisynthetic β-lactamase inhibitor which, in combination with ampicillin, extends the antibacterial activity of the latter to include some β-lactamase-producing strains of bacteria that would otherwise be resistant. The combination of sulbactam plus ampicillin for parenteral used clinically and bacteriologically effective in a variety of infections. The chemical linkage of sulbactam and ampicillin has now produced an orally effective compound, sultamicillin, with antibacterial activity and clinical efficacy which are similar to those of the parenteral formulation. Sultamicillin has been shown to be clinically effective in non-comparative trials in patients with infections of the respiratory tract, ears, nose and throat, urinary tract, skin and soft tissues, as well as in obstetric and gynaecological infections and in the treatment of gonorrhoea. While in several studies the incidence of diarrhoea associated with sultamicillin was greater than that with comparative antibacterials, sultamicillin-associated diarrhoea was generally mild and transitory, although occasionally severe enough to necessitate discontinuation of treatment. Further studies in larger groups of patients are needed to clarify the therapeutic efficacy and safety of sultamicillin in comparison with other antibacterial regimens and to determine the optimum single dosage for the treatment of gonorrhoea. Nonetheless, sultamicillin appears to provide a similar pharmacodynamic and pharmacokinetic profile to that of parenteral sulbactam plus ampicillin and, as such, will extend the therapeutic efficacy of ampicillin, with the further advantage of allowing treatment of patients with an oral formulation, thus avoiding the potentially adverse clinical and financial effects of prolonged parenteral therapy.

Sultamicillin is a mutual prodrug of ampicillin and sulbactam. Ampicillin, a semi-synthetic orally active broad spectrum antibiotic, is linked via a methylene group with a β-lactamase inhibitor. Sultamicillin is chemically oxymethyl penicillinate sulfone ester of ampicillin. After absorption, sultamicillin releases ampicillin and sulbactam into the system, so all the antibacterial efficacy of sultamicillin is due to ampicillin and sulbactam. Ampicillin exerts antibacterial activity against sensitive organisms by inhibiting biosynthesis of cell wall mucopeptide where as sulbactam irreversibly inhibits most important β-lactamases that occur in resistant strains. It is made by esterfication of sulbactam and ampicillin with methylene diol [$CH_2(OH)_2$] where one –COOH of sulbactam and one –COOH of ampicillin esterfies with two –OH of methylene diol to produce the desired mutual prodrug.[17]

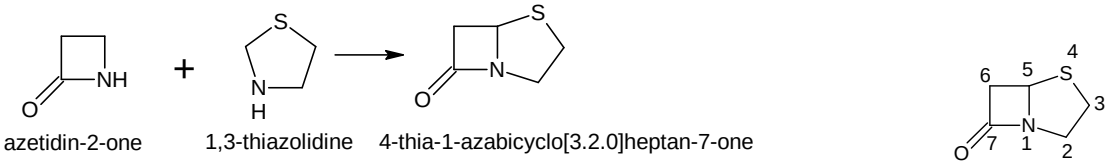

Figure-6: Carbopenam fused ring system.

All three moieties have same 4-thia-1-azabicyclo[3.2.0]heptan-7-one fused ring which is formed by fusion of azetidin-2-one with 1,3-thiazolidine. In heterocyclic ring system counting starts from Oxa (O)/Thia (S)/Aza (N) but in bicyclic fused ring nomenclature counting is reversed Aza (N)/Thia (S)/Oxa (O), so here nitrogen comes first (1-aza) in counting and for this sulphur is in 4th number (4-thia), so from right hand side after nitrogen 3 is for sulphur and from left hand side after sulphur nitrogen comes at 2 and both azetidin-2-one and 1,3-thiazolidine fuses at 0 so [3.2.0] is coming and 7 number comes from counting from nitrogen so heptan is coming. 4-thia-1-azabicyclo[3.2.0]heptan-7-one ring system comes then with 7th position is ketone (7-one).

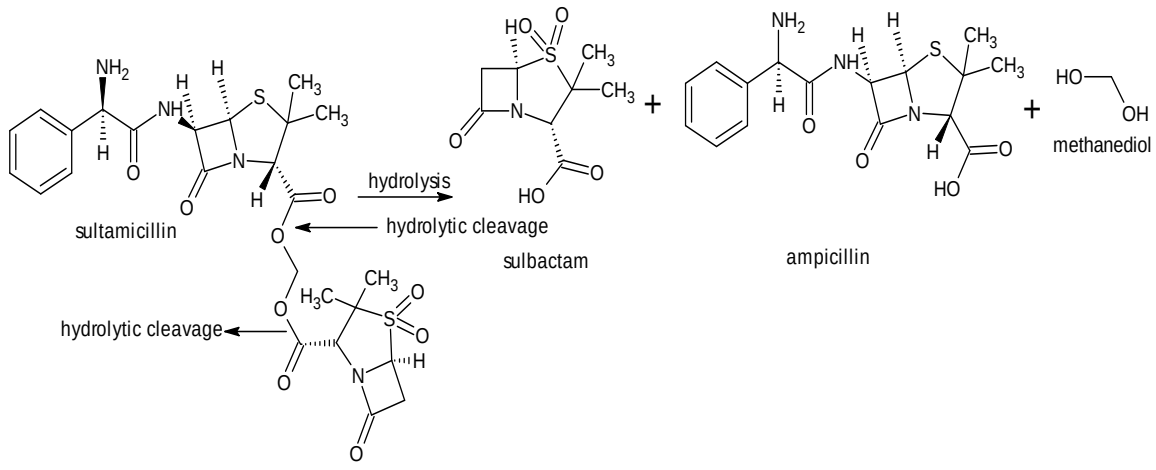

Figure-7: Sultamicillin hydrolyses in physiological fluid into it's two components: sulbactam & ampicillin.

Pharmacodynamic Properties: Biochemical studies with cell-free bacterial systems have shown sulbactam to be an irreversible inhibitor of most important β-lactamases that occur in penicillin-resistant 7 organisms. While sulbactam antibacterial activity is mainly limited to Neisseriacea, the potential for sulbactam sodium in preventing the destruction of penicillins and cephalosporins by resistant organisms was confirmed in whole organism studies using resistant strains, in which sulbactam sodium exhibited marked synergistic effects with penicillins and cephalosporins. Since sulbactam also binds to some penicillin-binding proteins, some sensitive strains are rendered more susceptible to the combination than to the β-lactam antibiotic alone. The bactericidal component of this product is ampicillin which, like benzyl penicillin, acts against sensitive organisms during the stage of active multiplication by the inhibition of biosynthesis of cell wall mucopeptide. Sultamicillin is effective against a wide range of gram-positive and gram-negative bacteria including: *Staphylococcus aureus* and *S. epidermidis* (including penicillin-resistant and some methicillin resistant strains); *Streptococcus pneumoniae*, *Streptococcus faecalis* and other Streptococcus species; *Haemophilus influenzae* and *H. parainfluenzae* (both β-lactamase positive and negative strains); *Moraxella catarrhalis*; anaerobes including *Bacteroides fragilis* and related species; *Escherichia coli*; *Klebsiella* species; *Proteus* species (both indole-positive and indole-negative); *Enterobacter* species; *Morganella morganii*; Citrobacter species; *Neisseria meningitidis* and *Neisseria gonorrhoeae*.

Pharmacokinetics Properties: Following oral administration in humans, sultamicillin is hydrolyzed during absorption to provide sulbactam and ampicillin in a 1:1 molar ratio in the systemic circulation. The bioavailability of an oral dose is 80% of an equal intravenous dose of sulbactam and ampicillin. Administration following food does not affect the systemic bioavailability of sultamicillin. Peak serum levels of ampicillin following administration of sultamicillin are approximately twice those of an equal dose of oral ampicillin. Elimination half-lives are approximately 0.75 and 1 hour for sulbactam and ampicillin respectively in healthy volunteers, with 50-75% of each agent being excreted in the urine unchanged. Elimination half-lives are increased in the elderly and in patients with renal dysfunction. Probenecid decreases the renal tubular secretion of both ampicillin and sulbactam. Concurrent use of probenecid with sultamicillin results in increased and prolonged blood levels of ampicillin and sulbactam.

CONCLUSION

A therapeutically significant drug may have limited utilization in clinical practice because of poor organoleptic properties, poor bioavailability, short duration of action, nonspecificity, incomplete absorption, poor aqueous solubility, high first-pass metabolism or other adverse effects. There is a great emphasis on research to discover methods aimed at improving their therapeutic efficacy by minimizing or eliminating these undesirable properties.

Sometimes, an adequate pharmaceutical formulation can overcome these drawbacks, but often the galenic formulation is inoperant and a chemical modification of active molecule is necessary to correct its pharmacokinetic insufficiencies.

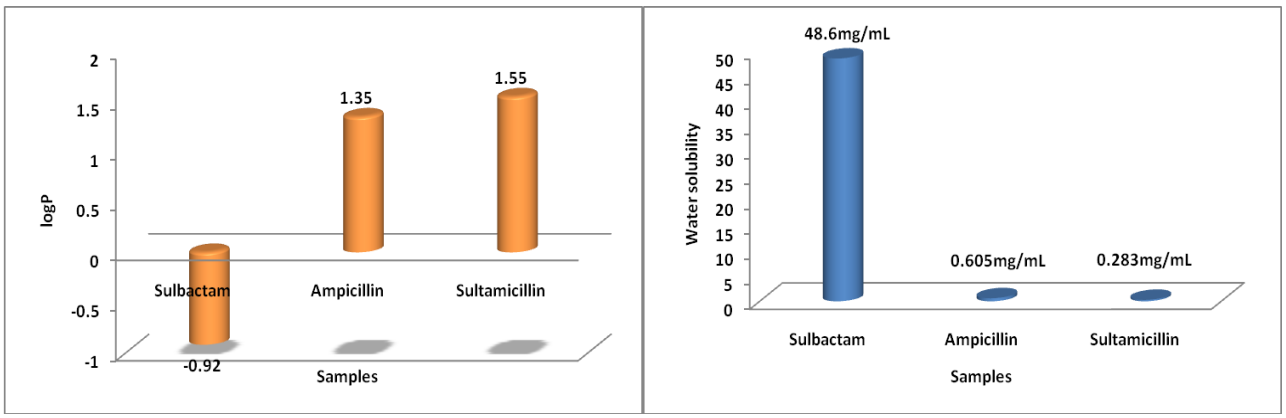

Figure-8: logP and solubility.

This chemical formulation process, whose objective is to convert an interesting active molecule into a clinically acceptable drug, often involves the so-called 'Prodrug design.' Mutual prodrug is a type of carrier-linked prodrug, where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa. Mutual prodrug design is really no different from the general drug discovery process, in which a unique substance is observed to have desirable pharmacological effects and studies of its properties lead to the design of better drugs. It is a very fruitful area of research and its introduction in human therapy has given successful results in improving the clinical and therapeutic effectiveness of drugs suffering from some undesirable properties that otherwise hinder their clinical usefulness.

The introduction of mutual prodrug in human therapy has given successful results in overcoming undesirable properties like absorption, nonspecificity, poor bioavailability and GIT toxicity. Mutual prodrug design is really no different from the general drug discovery process, in which a unique substance is observed to have desirable pharmacological effects and studies of its properties lead to the design of better drugs. The review of application of mutual prodrug design suggests that the gain in therapeutic benefit from such an approach may either be modest or marked. For well-accepted and useful drugs with minor undesirable properties, which canbe ameliorated through prodrug design, the gain is usually modest.

On the other hand, for the active compounds that suffer from severe limitations, like lack of site specificity, poor bioavailability or lack of particular activity, mutual prodrug design leads to a marked therapeutic gain. Thus, mutual prodrug approach offers a very fruitful area of research and an efficient tool for improving the clinical and therapeutic effectiveness of a drug that is suffering from some undesirable properties hindering its clinical usefulness otherwise.

logP parameters:
Sulbactam [polar: logP (-0.92)]<Ampicillin [semipolar: logP (1.35)]<Sultamicillin [nonpolar: logP (1.55)]

Water solubility parameters:
Sulbactam [highly soluble: 48.6mg/mL]>Amplicillin [sparingly soluble: 0.605mg/mL]>Sultamicillin [slightly soluble 0.283mg/mL]
Sultamicillin prodrug is formed by covalent (sigma) σ bond by salbactam+methylene diol+ampicillin in which salbactam and ampicillin are connected with methylene diol by single bond to make mutual prodrug which releases two active components salbactam and ampicillin by biotransformation (hydrolysis) because sultamicillin is a diester formed by salbactam and ampicillin with methylene diol. Sultamicillin is official as such and also as toluene sulphonic acid salt (Sultamicillin tosilate). The salt further improves physicochemical properties and makes it suitable for oral administration as 375 mg tablets.

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