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CHAPTER 14

Sulphonamides, Sulfones, and Folate Reductase Inhibitorss

14.1. SULPHONAMIDES

14.1.1. Introduction

Several groups of drugs are derived from **sulphonamides** (or **sulpha drugs**). These are synthetic antimicrobial agents containing sulphonamide group. However, some sulphonamides such as anticonvulsant sultiame lack antibacterial activity. Sulphonamides are used for preventing and treating bacterial infections, diabetes mellitus, oedema, hypertension, and gout. Sulfonylureas and thiazide diuretics are newer groups of drugs that are derived from antibacterial sulphonamides.

Sulphonamide was the first antimicrobial agent which acted against pyrogenic bacterial infections. Its molecular structure resembles to the structure of *p*-Aminobenzoic Acid (PABA), required as a substrate of dihydropteroate synthetase enzyme for synthesising Tetrahydrofolic acid (THF) in bacteria. Metabolic processes in bacteria requiring PABA are inhibited by the sulphonamides derived from sulphanilamide.

Allergies commonly occur on administering sulphonamides. Data shows that the adverse drug reactions related to sulpha antibiotics are 3%; so, they are prescribed cautiously. Sulpha drugs are different from other sulphur-containing compounds (such as sulphates and sulphites) which are not chemically related to sulphonamide group and also do not cause the hypersensitivity reactions caused by sulphonamides. Kernicterus (brain damage due to excess bilirubin) is a potential side effect of sulphonamide as it displaces bilirubin from albumin.

14.1.2. Historical Development

Sulphonamides were the first antimicrobial drugs that paved the way for antibiotic revolution in medicine. The first sulfonamide, trade named **Prontosil**, was a prodrug. Experiments with Prontosil began in **1932** in the laboratories of Bayer AG. The Bayer team believed that coal-tar dyes that bind to bacteria and parasites might be used to target harmful organisms in the body. After many unsuccessful trial-and-error works on hundreds of dyes, a team led by **Gerhard Domagk** (physician/researcher) found a dye that worked. It was a red dye, synthesised by Bayer chemist, **Josef Klarer** that remarkably prevents some bacterial infections in mice.

The first official communication about the discovery was not published until 1935, more than two years after **Klarer** and his research partner, **Fritz Mietzsch** patented the drug. Prontosil was the first discovered medicine that could treat various bacterial infections in human body. It had a strong protective action against infections caused by *Streptococci*, including blood infections, childbed

fever, and erysipelas. It has a lesser effect on the infections caused by other cocci. Later it was discovered by a French research team, led by **Ernest Fourneau**, at the Pasteur Institute that prontosil metabolised into two pieces inside the body, releasing **sulfanilamide** (a smaller, colourless, active compound) from the inactive dye portion (**figure 14.1**). This discovery established the concept of bioactivation and dashed the German corporation's dreams of [illegible] sulfanilamide was first synthesised in **1906** and was used in dye-making industries.

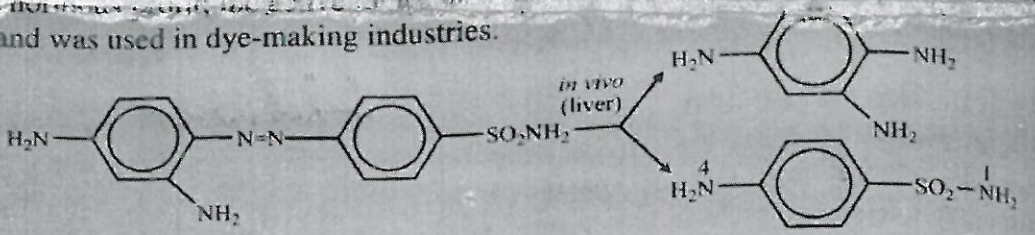
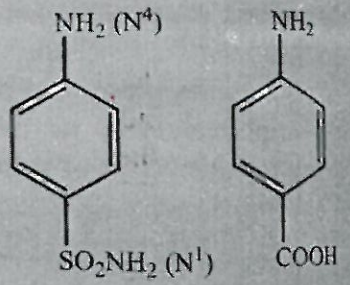


Figure 14.1: Metabolism of Prontosil

For several years in the **late 1930s**, numerous manufacturers produced thousands of tons of myriad forms of sulfa. **Sulfa drugs** being the first and only effective antibiotic available in the years before penicillin, continued to flourish through the early years of World War II. They saved the lives of many patients including Franklin Delano Roosevelt, Jr. (son of President Franklin Delano Roosevelt) (in 1936) and Winston Churchill. Sulfa had a central role in preventing wound infections during the war. American soldiers were issued a first-aid kit containing sulfa pills and powder and were told to sprinkle it on any open wound.

14.1.3. Chemistry

Chemically sulfa drugs are amphoteric. They behave as weak organic acid with pKa ranging from 4.79 to 8.56. They are weakly soluble in water, but their solubility increases at alkaline pH. Their sodium salts are easily soluble in water. Sulfacetamide has a neutral pH and is used in eye infections. The basic structure of sulfanilamide and PABA is given in **figure 14.2.**



Sulfanilamide PABA

Figure 14.2: Structures of Sulfanilamide and PABA

The nitrogen of amino group at *para* position in sulfanilamide is designated as N^4, and the nitrogen of SO_2NH_2 is designated as N^1. Systemic sulfa drugs are developed by substitution at N^1, and the gut active sulfa drugs are produced by substitution at N^4. Around 5000 compounds are synthesised by substituting at these two positions. Out of these compounds, 30 are clinically significant. Sulfanilamide and its derivatives are popularly known as sulfonamides or sulfa drugs.

14.1.4. Classification

Sulphonamides are classified as follows:

1) **Based on their Duration of Action**
   i) **Short Acting Sulphonamides:** These have 4-8 hours of duration of action, e.g., Sulphadiazine and Sulphamethoxazole.

ii) **Intermediate Acting Sulphonamides:** These have 8-16 hours of duration of action, **e.g.,** Sulphaphenazole and Sulphamethoxazole.

iii) **Long Acting Sulphonamides:** These have 1-7 days of duration of action, **e.g.,** Sulphaphenazole and Sulpha dimethoxine.

2) **Based on their Pharmacological Action**

i) Used in systemic infections, e.g., Sulphadiazine.

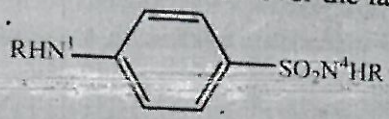
ii) Used in eye infections, **e.g.,** Sulphacetamide.

iii) Used in intestinal infections, **e.g.,** Sulphapyridine.

iv) Used in urinary tract infections, **e.g.,** Sulphamethoxazole.

14.1.5. SAR of Sulphonamides

Sulphonamides are an important chemical class, and had been investigated for their activity on infective organisms. In antibacterial therapy, they are placed next to antibiotics, sometimes even preferred over the latter.



The major features of SAR of sulphonamides include:

1) Sulphanilamide skeleton is the minimum structural requirement for antibacterial activity.

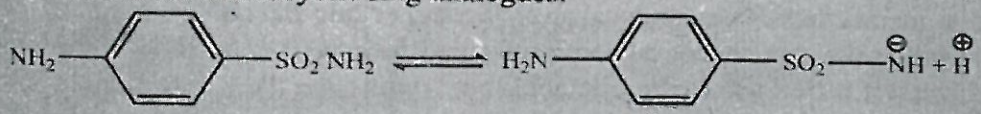
2) Sulphur atom should be directly linked to the benzene ring.

3) In N^1-substituted sulphonamides, nature of the substituent at amide group influences the activity.

4) Substituents that impart electron rich character to SO_2 group increase bacteriostatic activity.

5) Heterocyclic substituents give rise to highly potent derivatives.

6) Sulphonamides containing a single benzene ring at N^1-position are more toxic than the heterocyclic ring analogues.



Unionised Ionised

7) The free aromatic amino group should be present *para* to the sulphonamide group. Its substitution at *ortho* or *meta* position will give rise to compounds with no antibacterial activity.

8) Presence of free amino group is essential for activity. Any substitution of amino group either results in prodrug nature or in the loss of activity.

9) The sulphonamides are active in their ionised form. Their maximum activity is observed between 6.6 to 7.4 pKa values.

10) Substitutions in the benzene ring of sulphonamides give rise to inactive compounds.

11) Substitution of free sulfonic acid ($-SO_3H$) for sulphonamide function, destroys the activity; however, replacing with a sulfonic acid group ($-SO_2H$) and acetylation of N_4-position retains the activity.

14.1.6. Mechanism of Action

Sulphonamides are bacteriostatic when administered to humans in achievable doses. They inhibit dihydropteroate synthase enzyme, which is essential for the biosynthesis of folic acid derivatives, and ultimately, thymidine, which is required for DNA. They act by competing at the active site with *p*-aminobenzoic acid (PABA), which is a normal [illegible] component of folic acid derivatives. PABA gets incorporated into the developing tetrahydrofolic acid molecule by enzyme-catalysed condensation with 6-hydroxymethyl-7,8-dihydropterin-pyrophosphate to form 7,8-dihydropteroate and pyrophosphate. Thus, sulphonamides are also classified as antimetabolites (**figure 14.3**).

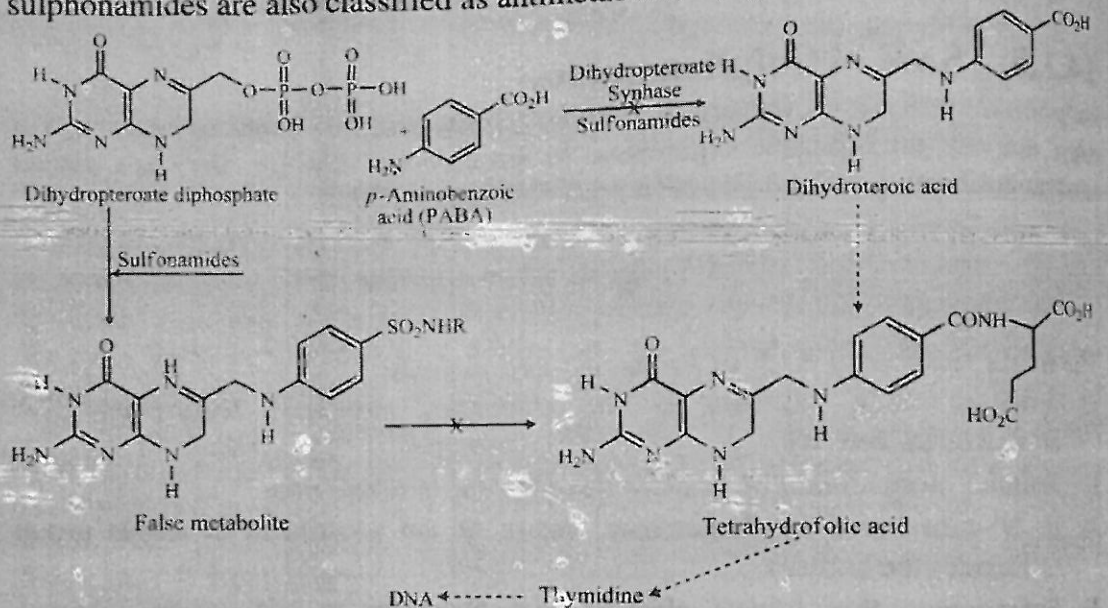


Figure 14.3: Microbial Biosynthetic Pathway Leading to Tetrahydrofolic Acid Synthesis and Major Site of Action of Sulphonamides as well as Site of Action Seen in Some Bacteria Resulting in Incorporation of Sulphonamide as a False Metabolite

The antimicrobial efficacy of sulphonamides can be reversed by adding significant quantities of PABA into the diet (in some multivitamin preparations and as metabolites of certain local anaesthetics) or into the culture medium. Most susceptible bacteria cannot take up preformed folic acid from their environment and convert it to a tetrahydrofolic acid; but, synthesise their own folates, which are essential intermediates for thymidine biosynthesis.

Without thymidine, bacteria fail to multiply. This inhibition is bacteriostatic as well as bactericidal. Humans cannot synthesise folates from component parts, because they lack the required enzymes, including dihydropteroate syntehase, and folic acid is supplied to us in our diet. Consequently, sulphonamides have no similarly lethal effect on human cell growth. The basis for the selective toxicity of sulphonamides thus is clear.

In few bacteria strains, sulphonamides bind to the dihydropteroate diphosphate, and forms an unnatural product which fails to undergo the required glutamic acid condensation. This false metabolite is an enzyme inhibitor, and the net result is inability of the bacteria to multiply as the pre-formed folic acid in their cells is used up and nucleic acid biosynthesis becomes impossible. Bacteria that are able to take up pre-formed folic acid into their cells are intrinsically resistant to sulphonamides.

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14.1.7. Uses

Sulfisoxazole acetyl along with erythromycin ethylsuccinate is the most popular sulphonamide combination. Sulfisoxazole acetyl is tasteless, and thus is used in pediatric preparations. Its acetyl moiety is removed in the GIT, giving rise to the active sulfisoxazole. Along with the surviving sulfonamides, it has a broad antimicrobial spectrum *in vitro* against gram-negative organisms, but it has a limited clinical use because of bacterial resistance develo[illegible] enterobacteriaceae (*Escherichia coli*, *Klebsiella sp.*, and *Proteus sp.*), *Streptococcus pyogenes*, *Streptococcus pneusmoniae*, and *Haemophilus sp* are the susceptible organisms.

Sulphamethoxazole along with trimethoprim is used for treating primary uncomplicated urinary tract infections.

The remaining sulphonamides are not used systemically. The **silver salt of sulphadiazine** is topically used for the treatment of burns and is effective against various bacteria and fungus. **Sulphacetamide** is ophthalmically used for treatment of eye infections caused by susceptible organisms. **Sulphasalazine** is a prodrug used in the treatment of ulcerative colitis and Crohn's disease.

14.1.8. Adverse Effects

The most common adverse effects of sulphonamides include allergic reactions that take the form of rash, photosensitivity, and drug fever. Less common problems are kidney and liver damage, haemolytic anaemia, and other blood problems. Most serious adverse effect is Stevens-Johnson syndrome, characterised by fatal erythema multiforme and ulceration of mucous membranes of eye, mouth and urethra. However, these effects occur rarely.

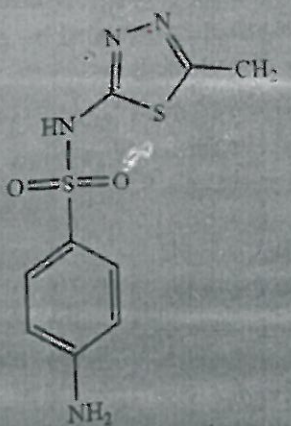
14.1.9. Important Products

The following drugs are studied in detail:

1) Sulphamethizole, 2) Sulfisoxazole, 3) Sulphamethazine,
4) Sulfacetamide, 5) Sulphapyridine, 6) Sulfamethoxazole,
7) Sulphadiazine, 8) Mafenide acetate, and 9) Sulfasalazine.

14.1.9.1. Sulphamethizole

Sulphamethizole is an antibacterial agent.



Sulphamethizole

Mechanism of Action

Sulphamethizole is a competitive inhibitor of bacterial dihydropteroate synthetase enzyme. It thus prevents the binding of *para*-aminobenzoic acid (PABA) substrate. This inhibited reaction is necessary in these organisms for folic acid synthesis.

Uses

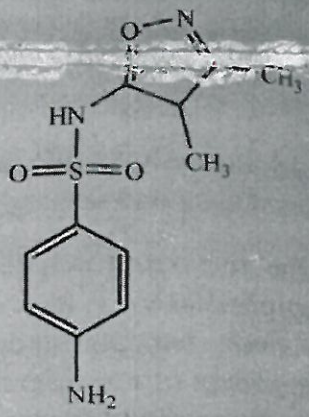
Sulphamethizole is used in the treatment of gram-negative bacterial infections, gram-positive bacterial infections, and urinary tract infections.

Adverse Effects

Common side effects of sulphamethizole include nausea, vomiting, diarrhoea, vaginitis, dermatitis, allergic reactions, skin rash, red or purple spots under the skin, blood in urine, and swelling of tongue, mouth, or rectum.

14.1.9.2. Sulfisoxazole

Sulfisoxazole is a short-acting sulfonamide antibacterial that shows activity against a wide range of gram-negative and gram-positive organisms.



Sulfisoxazole

Mechanism of Action

Sulfisoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. It inhibits bacterial synthesis of dihydrofolic acid by preventing the condensation of pteridine with *para*-aminobenzoic acid (PABA, a substrate of dihydropteroate synthetase enzyme). This inhibited reaction is necessary in these organisms for folic acid synthesis.

Uses

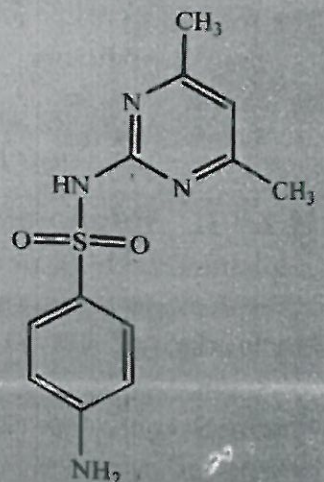
Sulfisoxazole is used for the treatment of severe, repeated, or long-lasting urinary tract infections, meningococcal meningitis, acute otitis media, trachoma, inclusion conjunctivitis, nocardiosis, chancroid, toxoplasmosis, malaria, and other bacterial infections.

Adverse Effects

Common side effects of sulfisoxazole include stomach pain, bloating, gas, headache, dizziness, ringing in ears, or swollen, black tongue.

14.1.9.3. Sulphamethazine

Sulphamethazine is a sulfanilamide anti-infective agent. Its spectrum of antimicrobial activity is similar to that of other sulfonamides.



Sulphamethazine

Mechanism of Action

Sulphamethazine inhibits the enzymatic conversion of pteridine and *p*-aminobenzoic acid (PABA) to dihydropteroic acid by competing with PABA for binding to dihydrofolate synthetase, which is an intermediate of tetrahydrofolic acid (THF) synthesis. THF is required for the synthesis of purines and dTMP, and thus inhibition of its synthesis retards bacterial growth.

Uses

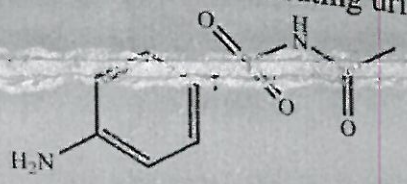
Sulphamethazine is used for the treatment of bacterial infections causing bronchitis, prostatitis, and urinary tract infections.

Adverse Effects

Common side effects of sulphamethazine include diarrhoea, dizziness, nausea, head pain, itching, loss of appetite, rash, and sluggishness.

14.1.9.4. Sulfacetamide

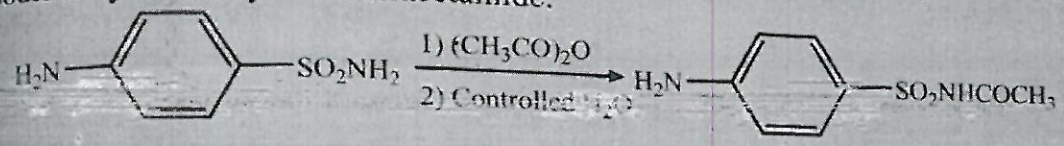
Sulfacetamide is a sulphonamide antibacterial agent that is topically used for treating skin infections and orally used for treating urinary tract infections.



Sulfacetamide

Synthesis

Reaction of 4-aminobenzene sulphonamide with acetic anhydride and subsequent selective, reductive deacylation of the resulting acetamide using a system of zinc-sodium hydroxide yields sulfacetamide.



Mechanism of Action

Sulfacetamide is a competitive inhibitor of bacterial *para*-aminobenzoic acid (PABA), which is essential for bacterial growth. This inhibited reaction is necessary in these organisms for folic acid synthesis.

Uses

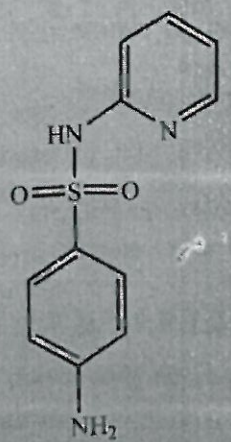
Sulfacetamide is used for treating bacterial vaginitis, keratitis, acute conjunctivitis, and blepharitis.

Adverse Effects

The adverse effects of sulfacetamide include severe allergic reactions (rash hives; itching; difficulty breathing; tightness in chest; swelling of mouth, face, lips, or tongue), cracked or extremely dry skin, fever, joint pain, severe diarrhoea, sores in mouth, yellowing of skin or eyes, and red, swollen, scaling, or blistered skin

14.1.9.5. Sulphapyridine

Sulphapyridine is an antibacterial, potentially toxic, and previously used to treat certain skin diseases. However, it is no longer prescribed.



Sulphapyridine

Mechanism of Action

Sulphapyridine is a competitive inhibitor of bacterial dihydropteroate synthetase enzyme. This inhibited reaction is necessary in these organisms for folic acid synthesis by processing the substrate *para*-aminobenzoic acid (PABA). Dihydropteroate synthetase activity is required in the synthesis of folate, which is required for cells to make nucleic acids; and, if DNA molecules cannot be built, the cell cannot divide.

Uses

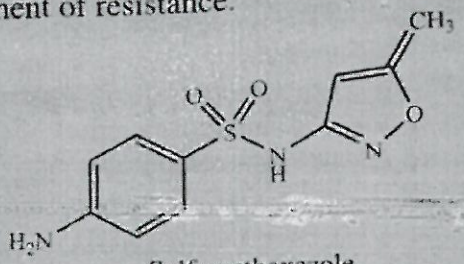
treatment of dermatitis herpetiformis, benign

Adverse Effects

More common side effects of sulphapyridine include fever, headache, itching, and skin rash. Less common side effects include aching of joints and muscles, difficulty in swallowing, sore throat, unusual bleeding or bruising, unusual tiredness or weakness, yellow eyes or skin, pale skin, and redness, blistering, peeling or loosening of skin.

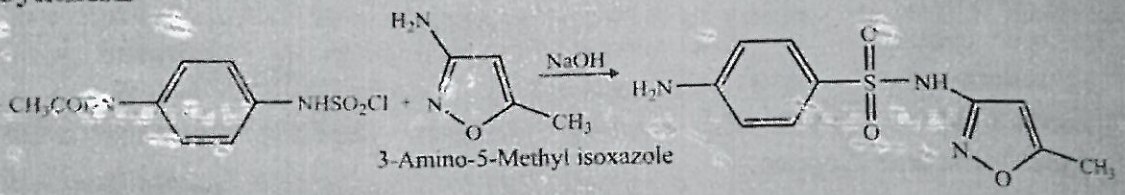
14.1.9.6. Sulfamethoxazole

Sulfamethoxazole is a bacteriostatic antibacterial agent that interferes with folic acid synthesis in susceptible bacteria. Its broad spectrum of activity has been limited by the development of resistance.



Sulfamethoxazole

Synthesis



3-Amino-5-Methyl isoxazole

Mechanism of Action

Sulfamethoxazole inhibits the enzymatic conversion of pteridine and *p*-aminobenzoic acid (PABA) to dihydropteroic acid by competing with PABA for binding to dihydrofolate synthetase, which an intermediate of tetrahydrofolic acid (THF) synthesis. THF is essential for the synthesis of purines and dTMP, and inhibition of its synthesis inhibits bacterial growth.

Uses

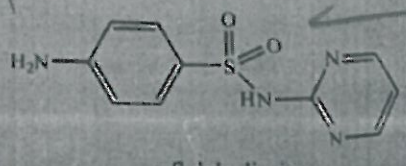
Sulfamethoxazole is used for the treatment of bacterial infections causing bronchitis, prostatitis, and urinary tract infections.

Adverse Effects

The adverse effects of sulfamethoxazole include fever, itching, rash, and dizziness.

14.1.9.7. Sulphadiazine

Sulphadiazine is a short-acting bacteriostatic and a synthetic pyrimidinyl sulfonamide derivative.



Sulphadiazine

Mechanism of Action

Sulphadiazine is a competitive inhibitor of bacterial enzyme dihydropteroate synthetase, which is required for proper processing of *para*-aminobenzoic acid (PABA), which is essential for folic acid synthesis. This inhibited reaction is necessary in these organisms for folic acid synthesis.

Uses

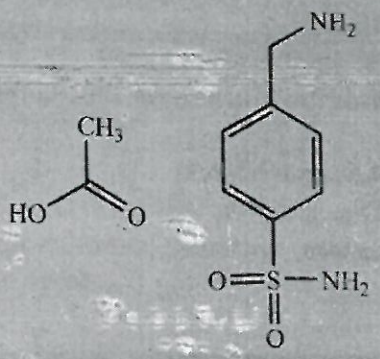
1) Sulphadiazine can be used for the treatment of upper respiratory tract infections, otitis media, *Meningococcal* meningitis, boils carbuncle, puerperal fever, urinary tract infections, acute dysentery, etc.
2) It is also used for treating infections caused by *Haemolytic streptococcus*, *Neisseria gonorrhoea*, and *E. coli*.

Adverse Effects

The adverse effects of sulphadiazine include anxiety, blurred vision, changes in menstrual periods, chills, cold sweats, coma, confusion, cool, pale skin, decreased sexual ability in males, and depression.

14.1.9.8. Mafenide Acetate

Mafenide is a sulfonamide-type antimicrobial agent that is used to treat severe burns. It reduces bacterial population in the burn tissue and promotes healing of deep burns.



Mafenide Acetate

Mechanism of Action

The precise mechanism of mafenide is not known. However, it is assumed to reduce the bacterial population in avascular burn tissue and promote spontaneous healing of deep burns.

Uses

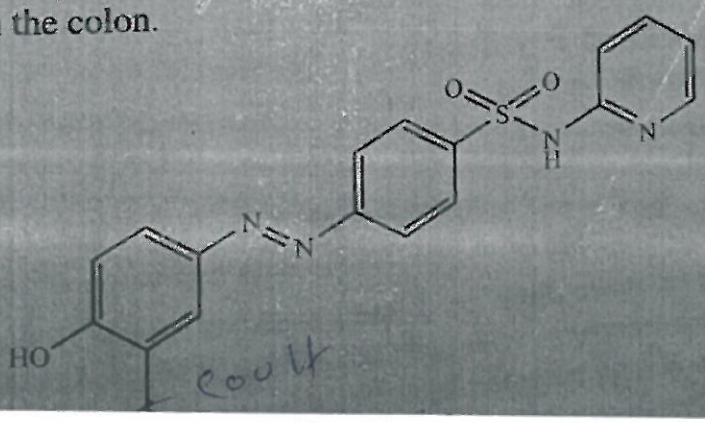
Mafenide is used as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds.

Adverse Effects

Common side effects of mafenide include rash, redness, blistering, or itching of treated skin; pain or burning of treated skin; or white or pruned appearance of the skin (caused by leaving wound dressings on for long periods of time).

14.1.9.9. Sulfasalazine

Sulfasalazine is a drug that is used in the management of inflammatory bowel diseases. Its activity lies in its metabolic breakdown product, 5-aminosalicylic acid, released in the colon.



Mechanism of Action

The mode of action of sulfasalazine or its metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP), is still unknown, but may be related to anti-inflammatory and/or immunomodulatory properties in animal and *in vitro* models, to its affinity for connective tissue, and/or to the relatively high concentration in serous fluids, liver and intestinal walls, as demonstrated in autoradiographic studies in animals.

In ulcerative colitis, clinical studies with rectal administration of sulfasalazine, SP and 5-ASA have indicated that the major therapeutic action resides in the 5-ASA moiety. Relative contribution of the parent drug and the major metabolites in rheumatoid arthritis is unknown.

Uses

Sulfasalazine is used for the treatment of Crohn's disease and rheumatoid arthritis as a second-line agent.

Adverse Effects

The common side effects of sulfasalazine include decreased appetite, headache, nausea, vomiting, stomach upset and pain, rash, itching, decreased sperm count (only while taking the drug), and dizziness.

14.2. FOLATE REDUCTASE INHIBITORS

14.2.1. Introduction

2,4-Diamino pyrimidine derivatives, like trimethoprim and pyrimethamine, inhibit DHFR enzyme of bacteria and plasmodium, respectively. DHFR converts dihydrofolic acid to tetrahydrofolic acid, which in turn converts into folate cofactors. These drugs inhibit DNA synthesis and cell division.

Sulphonamides and trimethoprim are used in the treatment and prevention of infections. Combination of sulphadiazine and trimethoprim is used in UTIs. Combination of sulphamethoxazole and trimethoprim (cotrimoxazole) is used in bronchitis, middle ear infection, UTI, traveller's diarrhoea, and also in prevention and treatment of Pneumocystis Carinii Pneumonia (PCP).

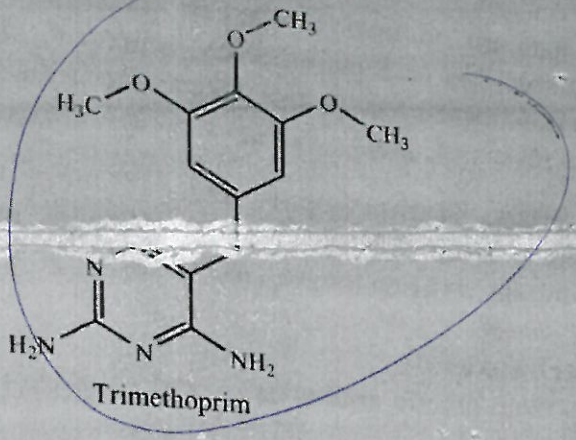
14.2.2. Important Products

The following drugs are studied in detail:

1) Trimethoprim, and
2) Cotrimoxazole.

14.2.2.1. Trimethoprim

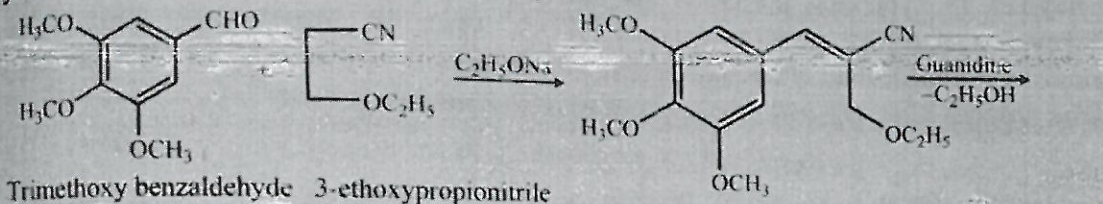
Trimethoprim is a pyrimidine inhibitor of dihydrofolate reductase. It is an antibacterial which interferes with folic acid metabolism and causes a depression of hematopoiesis. It is potentiated by sulfonamides, and is most often used along with sulfamethoxazole.



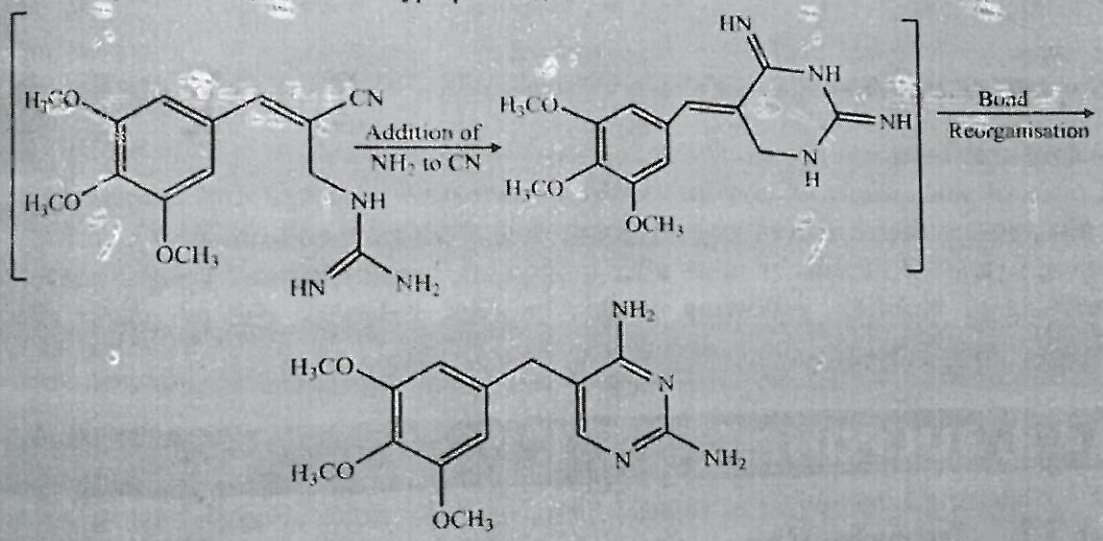
Trimethoprim

Synthesis

3,4,5-Trimethoxybenzaldehyde is condensed with 3-ethoxypropionitrile to give the corresponding benzylidene derivative, which directly reacts with guanidine to yield trimethoprim.



Trimethoxy benzaldehyde 3-ethoxypropionitrile



Mechanism of Action

Trimethoprim inhibits dihydrofolate reductase enzyme, and prevents the conversion of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF) in thymidine synthesis pathway. The affinity of its action on bacterial dihydrofolate reductase is thousand times more than that on human dihydrofolate reductase.

Uses

1) Trimethoprim is used for the treatment of UTIs, uncomplicated pyelonephritis (with sulfamethoxazole), and mild acute prostatitis.
2) It is also used as pericoital (with sulfamethoxazole) or continuous prophylaxis in females with recurrent cystitis.
3) It is useful as an alternative in treating asymptomatic bacteriuria during pregnancy (only before the last 6 weeks of pregnancy).

4) Its other uses are alternative agent in respiratory tract infections (otitis, sinusitis, bronchitis and pneumonia), treatment of pneumonia (acute or prophylaxis), Nocardia infections, and traveller's diarrhoea.

Adverse Effects

Common side effects of trimethoprim include itching, rash, diarrhoea, nausea, vomiting, stomach upset, loss of appetite, changes in taste, headache, skin sensitivity to sunlight, swollen tongue [illegible]

14.2.2.2. Cotrimoxazole

Cotrimoxazole is a synthetic antibacterial, and combination of sulfamethoxazole and trimethoprim.

Mechanism of Action

Cotrimoxazole is a bactericidal, and acts by sequential blockade of folic acid enzymes in synthesis pathway. Its sulfamethoxazole component inhibits the formation of dihydrofolic acid from PABA, while its trimethoprim component inhibits dihydrofolate reductase. Both the drugs inhibit folic acid synthesis, and thus prevent bacterial cell synthesis of essential nucleic acids.

Uses

Cotrimoxazole is effective against *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus mirabilis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Acinetobacter*, *Salmonella*, *Shigella*, and *P. carinii*.

Adverse Effects

Common side effects of cotrimoxazole include rash, itching, sore throat, fever, chills, severe diarrhoea (watery or bloody stools with or without fever), stomach cramps (up to 2 months or more after treatment), breathlessness, cough, unusual bruising or bleeding, yellowing of skin or eyes, paleness, red or purple skin discolorations, and joint or muscle pain.

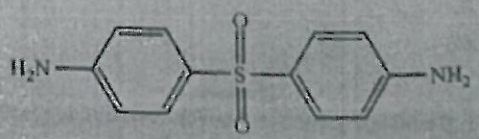
14.3. SULFONES

14.3.1. Introduction

Studies have suggested that there are about 11 million cases of leprosy in world, of which 60% are in Asia (with 3.5 million in India alone). Diaminodiphenyl sulphone (dapsone) is used for the treatment of infection caused by *Mycobacterium leprae*.

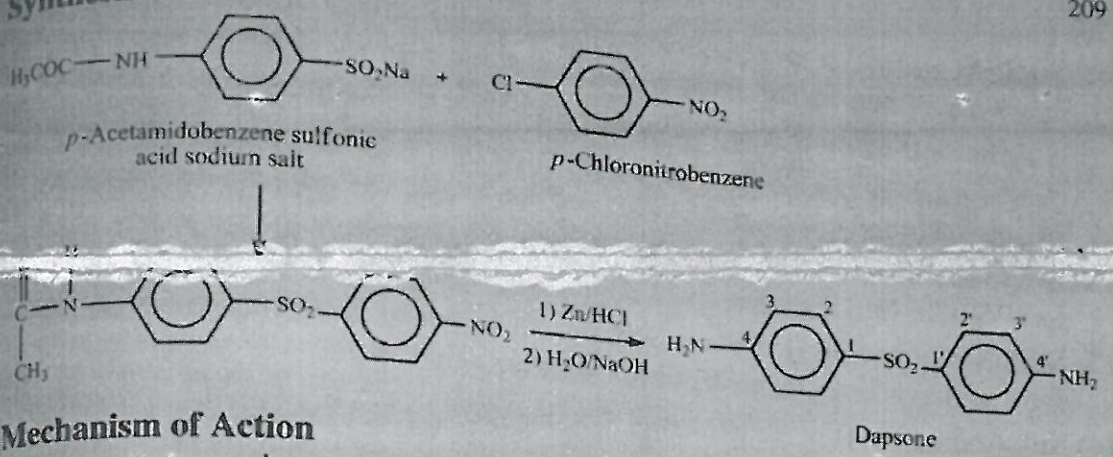
14.3.2. Dapsone

Dapsone is a nearly water-insoluble agent that is very weakly basic (pK_a ~ 1.0). Its lack of solubility is somewhat responsible for the occurrence of gastrointestinal irritation. Even if dapsone is poorly soluble, it gets efficiently absorbed from the GIT. Although dapsone is bound to plasma protein (~70%), it is distributed throughout the body.



4,4'-Diaminodiphenylsulphone (Dapsone)

Synthesis



Mechanism of Action

Dapsone acts against bacteria and protozoa by inhibiting the synthesis of dihydrofolic acid through competition with *para*-amino-benzoate for the active site of dihydropteroate synthetase. The anti-inflammatory action of dapsone is unrelated to its antibacterial action and is still not fully understood.

Uses

1) Dapsone is used to control dermatologic symptoms of dermatitis herpetiformis.
2) It is used alone or with other anti-leprosy drugs for leprosy.
3) It is also used to prevent malaria, certain types of arthritis or other inflammatory conditions, or *Pneumocystis Carinii* Pneumonia (PCP).

Adverse Effects

The adverse effects of dapsone include allergic reactions (difficulty in breathing; swelling of lips, tongue, or face; or hives), bluish skin colour, muscle weakness, numbness or tingling, abdominal pain, dark coloured urine or pale coloured stools, and unusual tiredness.

14.4. SUMMARY

The details given in the chapter can be summarised as follows:

1) Several groups of drugs are derived from **sulphonamides** (or **sulpha drugs**). These are synthetic antimicrobial agents containing sulphonamide group.
2) **Sulphonamide** was the first antimicrobial agent which acted against pyrogenic bacterial infections.
3) The first sulfonamide, trade named **Prontosil**, was a prodrug.
4) Chemically sulfa drugs are amphoteric.
5) **Sulfisoxazole acetyl along with erythromycin ethylsuccinate** is the most popular sulphonamide combination.
6) **Sulphamethoxazole along with trimethoprim** is used for treating primary uncomplicated urinary tract infections.
7) The **silver salt of sulphadiazine** is topically used for the treatment of burns and is effective against various bacteria and fungus.
8) **Sulphamethizole** is a competitive inhibitor of bacterial dihydropteroate

6) **Based on their Source**
   i) **Fungi:** Penicillin, Griseofulvin, and Cephalosporin.
   ii) **Bacteria:** Polymyxin B, Tyrothricin, Colistin, Aztreonam, and Bacitracin.
   iii) **Actinomycetes:** Aminoglycosides, Macrolides, Tetracyclines, Polyenes, and Chloramphenicol.

1.2. β-LACTAM ANTIBIOTICS

1.2.1. Introduction

The β-lactam antibiotics belong to a broad category in which all the antibiotics have a β-lactam nucleus in their molecular structure, i.e., members of this antibiotic class possess a highly reactive 3-carbon and 1-nitrogen ring. The β-lactam antibiotics include penicillin derivatives (penams), monobactams, carbapenems and cephalosporins (cephems). They are the most widely used among all the antibiotics and act by inhibiting the cell wall synthesis of the bacterial organism.

The β-lactam antibiotics are generally given with β-lactamase inhibitors (e.g., clavulanic acid) because the bacteria obtain resistance to β-lactam antibiotics by producing β-lactamase enzyme which attacks the β-lactam ring.

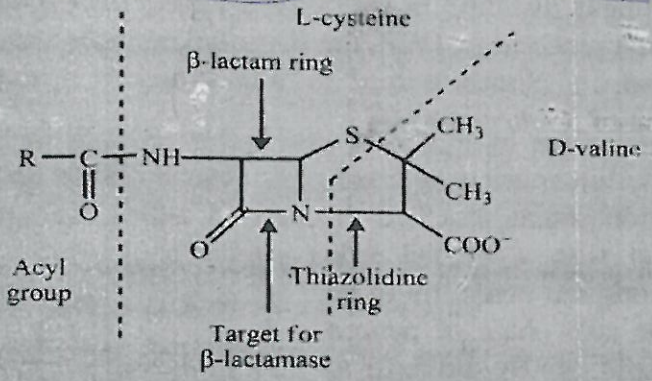


Figure 1.1: Antimicrobials that Interfere with Bacterial Nucleic Acids

1.2.2. Nomenclature

Based on their core ring structures, the β-lactam antibiotics are named as follows:

1) β-Lactams fused to saturated five-membered rings:
   i) **Penams:** β-Lactams containing thiazolidine rings.
   ii) **Carbapenams:** β-Lactams containing pyrrolidine rings.
   iii) **Oxapenams or Clavams:** β-Lactams fused to oxazolidine rings.
2) β-Lactams fused to unsaturated five-membered rings:
   i) **Penems:** β-Lactams containing 2,3-dihydrothiazole rings.
   ii) **Carbapenems:** β-Lactams containing 2,3-dihydro-1H-pyrrole rings.
3) β-Lactams fused to unsaturated six-membered rings:
   i) **Cephems:** β-Lactams containing 3,6-dihydro-2H-1,3-thiazine rings.
   ii) **Carbacephems:** β-Lactams containing 1,2,3,4-tetrahydropyridine rings.
   iii) **Oxacephems:** β-Lactams containing 3,6-dihydro-2H-1,3-oxazine rings.
4) **Monobactams:** β-Lactams not fused to any other ring.

1.2.3. Classification

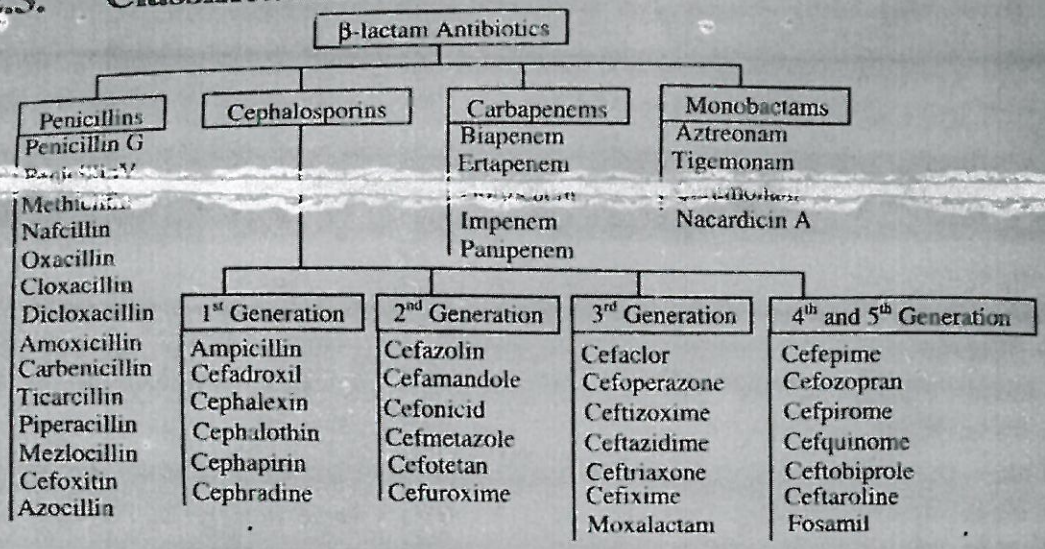


Figure 1.2: Classification of β-Lactam Antibiotics

1.2.4. Penicillin

Penicillin is the **first antibiotic** which was discovered in **September 1928 by Sir Alexander Fleming** (an English Bacteriologist). He accidentally obtained this antibiotic from a fungus dwelling in soil, called *Penicillium notatum*; however, its invention was first reported in **1929**, the first clinical trials were conducted on humans in **1940**, and was clinically used in **1941**. Presently it is obtained from a high yielding mutant of *P. chrysogenum*.

The nucleus of penicillin consists of fused rings of thiazolidine and *β*-lactam, and these rings have side chains attached through an amide linkage (**figure 1.3**). Penicillin G (PnG) with a benzyl side chain (at R) is the original penicillin to be used clinically. The side chain of natural penicillin can be split off by amidase to yield 6-amino-penicillanic acid, and then other side chains can be attached to yield different semi-synthetic penicillins having exclusive antibacterial properties and different pharmacokinetic profiles.

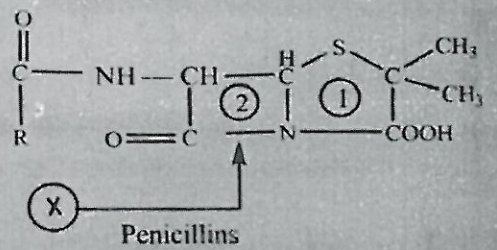


Figure 1.3: Chemical Structure of Penicillins. 1) Thiazolidine Ring; 2) β-Lactam Ring; (X) Bond which is Broken by Penicillinase.

Thiazolidine ring has a carboxyl group attached, to which salt formation occurs with Na^+ and K^+ ions. The stability of these salts is more stable than that of the parent acid. Sodium PnG is highly water-soluble, is stable in the dry state; however, its solution form rapidly deteriorates at room temperature, though it remains stable for 3 days at 4°C. Therefore, PnG solutions are recommended to prepare fresh.

1.2.4.1. Historical Background

Some historical aspects of penicillin are as follows:

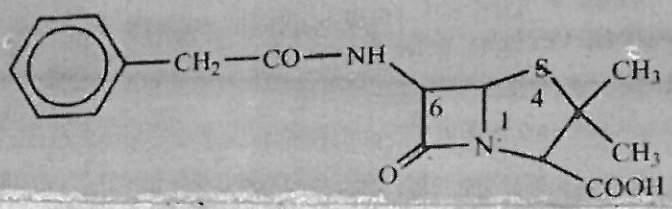
1) **Alexander Fleming** was born on 6 August, 1881 in Scotland in a farming family. He studied at Regent Street Polytechnic after his family moved to London in 1895.

2) He joined St. Mary's medical school and became research assistant to famous **Sir Almroth Wright**, after he got distinction in 1906.
3) He completed his MBBS degree with gold medal in 1908 from the University of London and worked as a lecturer at St. Mart till 1914.
4) He served as captain during the World War-I and worked in battlefield hospitals in France. After the war he returned to St. Mary in 1918 and was elected as Professor of Bacteriology in 1928.
5) In **1921**, he discovered natural antiseptic enzyme and named it as **lysozyme**. This substance existed in tissues and secretions like mucus, tears and egg-white but it did not have much effect on the strongly harmful bacteria.
6) In **1928** while experimenting on influenza virus in his laboratory in the basement of St. Mary's Hospital in London, he accidentally observed that a common fungus inhibits the growth of organism.
7) On September 28, 1928, he left one of his culture petri dishes with its lid opened for a few weeks. Consequently, a fungal spore landed on it, thus contaminating the culture. After returning, he noticed that his ***Staphylococcus*** culture was contaminated with the fungus.
8) However, he did not throw away the petri dish, instead examined it carefully. He observed that there was an inhibited bacterial growth around the mould (fungal colony).
9) He established that the mould was releasing an antibacterial substance that was spreading in the nearby area and lysing the bacteria, thus the bacterial colonies were dying.
10) He grew a pure culture and discovered that it was a Penicillium mould, which is now known as ***Penicillium notatum***.
11) He anticipated that Penicillium mould must be secreting an antibacterial substance, which he isolated in crude form of the active substance and named it **penicillin**.
12) This newly discovered active substance (penicillin) was effective even when diluted up to 800 times.
13) But the substance was also unstable and Alexander Fleming was not able to perform its isolation and purification. Therefore, he concluded that due to its instability, penicillin cannot be used clinically.
14) **Florey** and **Chain** in **1938** isolated pure form of penicillin, i.e., penicillenic by the processes of freeze-drying and chromatography.
15) **Fleming, Florey**, and **Chain** shared the Nobel Prize for this medicinal work on penicillin in **1945**.

1.2.4.2. Nomenclature

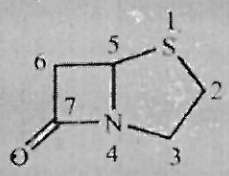
Penicillins are named as follows:

1) **Chemical Abstract:** Penicillins are described as 4-thia-1-azabicyclo-[3.2.0]-heptanes. Benzylpenicillin is described as 6-(2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabiclo-[3.2.0]-hept-2-ane-2-carboxylic acid.



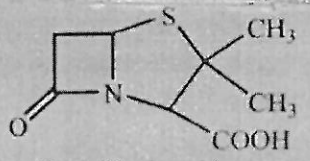
USP

2) **Penam:** The unsubstituted bicyclic ring system of penicillin is given the name penam, according to which the penicillins are described as 6-acylamino-2,2-dimethylpenam-3-carboxylates.



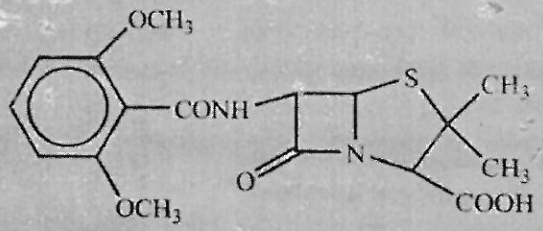
Penam

3) **Penicillanic Acid Derivatives**

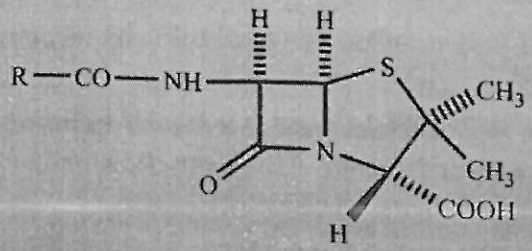


Penicillanic acid

4) **Mecillicillin is 2,6-Dimethoxy Benzamido Penicillanic Acid**

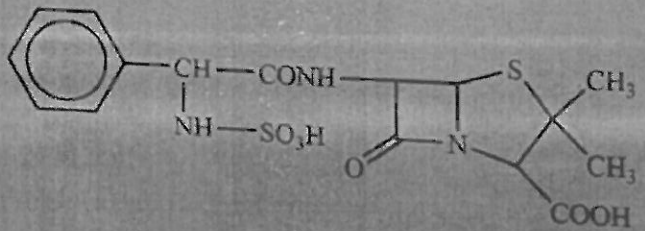


5) **Configuration:** Hydrogen atoms on the β-lactam ring, the acylamino groups are β, the carboxy group is α.



3S : 5R : 6R

6) **Penicillin Derivatives:** Semicillin is described as D-α-(sulfoamino) benzyl penicillin.

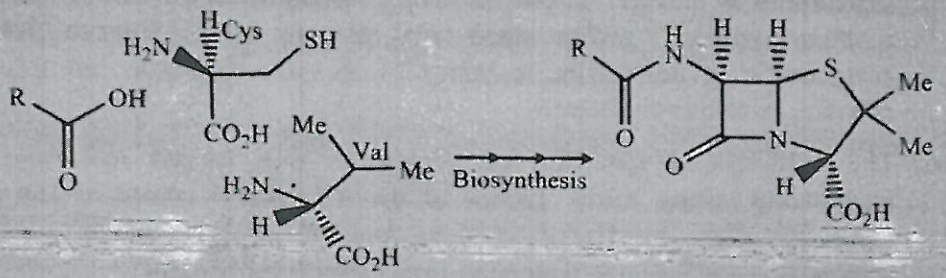


1.2.4.3. Stereochemistry

Penicillin molecule has three chiral carbon atoms at C-3, C-5 and C-6. The absolute configuration of all natural and synthetic penicillins about these three centres is the same. The 6th carbon atom bearing the acyl amino group has the L-configuration, whereas the carbon with carboxyl group has the D-configuration.

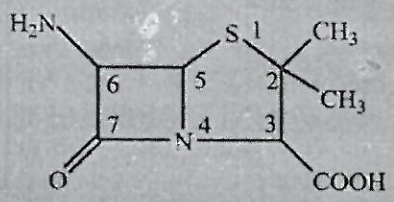
Thus, the acyl amino group and carboxyl group are *trans* to each other, with the former in α and the latter in β [illegible] relative to the β-lactam ring.

The absolute stereochemistry of penicillins was designated as **3S:5R:6R**. The atoms constituting 6-aminopenicillanic acid are biosynthetically derived from L-cysteine and D-valine amino acids.



1.2.4.4. Structure-Activity Relationship

The SAR of penicillin involves substitution of the following groups at the following positions of carbon atom:



1) **C-6 Amino West-End Substitution**

i) Design and development of the west-end substituents strengthened various weaknesses that have hampered penicillin's activity, stability, resistance, absorption, and distribution.

ii) C-6 amine moiety is required for the desired antibacterial activity, but substitution of amine via monoacylation provides more potent congeners.

iii) Only carboxamido derived west-end moieties are tolerated; sulphonation or phosphoramide-containing substituents lack antibacterial activity. Similarly, imide- or carbamate-containing west-end moieties are inferior.

iv) Agents that were stable to penicillinase enzymes were formed by introducing a more crowded environment around β-lactam moiety. Methicillin contains 2,6-dimethoxy benzamido west-end and the position of methoxy groups on the aromatic ring is important; the bis ortho arrangement leads to the most effective crowding around the β-lactam carbonyl centre, and retains the desired activity.

The oxacillins have a 5-methyl-3-phenyl-4-isoxazolyl west-end substituent that results in a crowded environment around the β-lactam ring. In these compounds, the methyl and phenyl substituents are positioned near to the β-lactam system. Removal of any of the two groups increases susceptibility to penicillinases.

v) The antibacterial spectrum of penicillins was enhanced by designing more hydrophilic west-end substituents that can enhance the potency against gram-negative pathogens. Ampicillin contains a D-α-aminophenylacetamido west-end and is recognised as amino penicillins. Substituents on the phenyl ring are harmful either due to decreased hydrophilicity or due to adverse polar effects if an ionisable substituent is present. These opposing forces are balanced by putting a *para*-hydroxyl group onto the phenyl ring. Amoxicillin is comparable to ampicillin in terms of *in vitro* potency, but its oral efficacy is relatively better.

vi) The antibacterial spectrum of penicillins was further enhanced by introducing strong acidic groups at the α-carbonyl centre of the side chain. These groups offered potency against *P. aeruginosa*. Carbenicillin possesses α-carboxyphenylacetamido west-end substituent.

vii) Acylation of the ampicillin west-end amine functionality with polar groups forms cyclic urea derivatives, i.e., ureido penicillins (azlocillin) containing a five-membered cyclic urea joined to the α-amino substituent of ampicillin via N-acylation.

The activity of azlocillin against *P. aeruginosa* is more than that of carbenicillin, and it is also potent against other gram-negative pathogenic species. Presence of urea group improves penetration into these gram-negative species that were previously resistant to penicillins.

2) **Substitutions at Sulphur:** Sulphur atom is placed at position 1 of penicillin to retain the desired antibacterial activity.

3) **C-2 Substituents:** The geminal dimethyl group at C-2 is characteristic of the penicillin.

4) **C-3 Substituents:** Derivatisation of the C-3 carboxylic acid group is not tolerated unless the free penicillin carboxylic acid can be generated *in vivo*. Doubly activated penicillin esters, such as alkanoyloxyalkyl congeners undergo rapid *in vivo* cleavage and generate active penicillin, e.g., pivampicillin and becampicillin.

5) **Variation at N-4:** Nitrogen atom at the ring junction is essential for antibacterial activity. It contributes to the reactivity of β-lactam carbonyl centre.

1.2.4.5. Chemical Degradation

In strongly acidic solutions (pH<3), penicillin undergoes a complex series of reactions and produce various inactive degradation products. Penicillinase enzyme hydrolyses the β-lactam ring and produces inactive **penicilloic acid**.

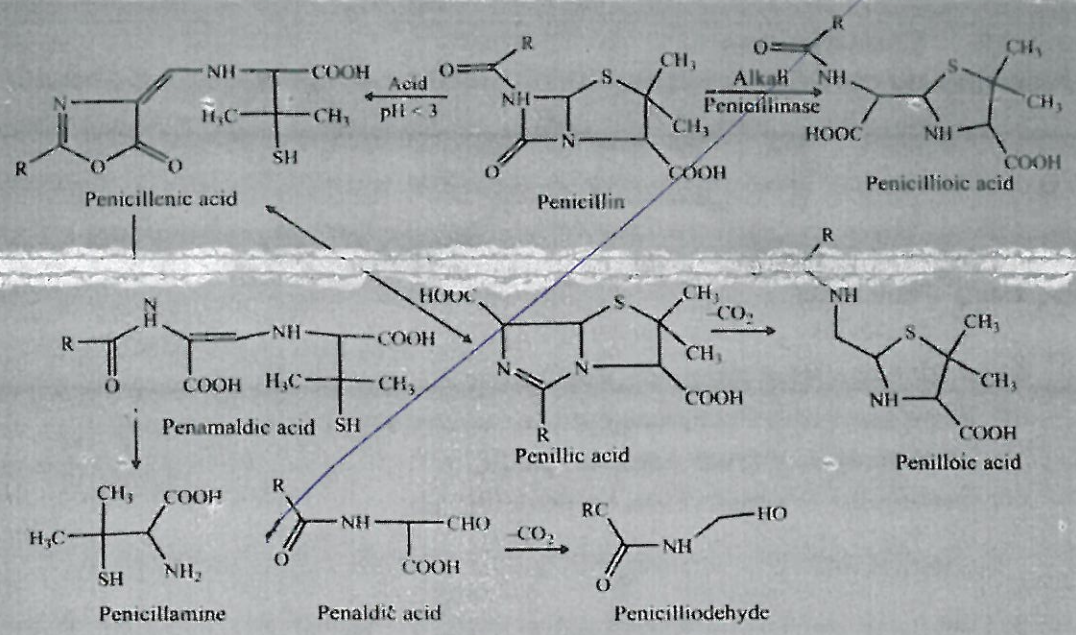


Figure 1.4: Chemical Degradation of Penicillin's

Acid-catalysed degradation of penicillin in stomach leads to its poor oral absorption. Thus, efforts to obtain penicillin with improved pharmacokinetic and microbiologic profile require to find acyl functionalities that minimise sensitivity of β-lactam ring to acid hydrolysis, and also maintain the antibacterial activity.

On substituting an electron-withdrawing group at the α-position of benzyl penicillin, the penicillin gets stabilised to acid-catalysed hydrolysis. The increased stability offered by such electron-withdrawing groups decreases the reactivity of the side chain amide carbonyl oxygen atom towards participation in β-lactam ring opening to form penicillenic acid.

1.2.4.6. Mechanism of Action

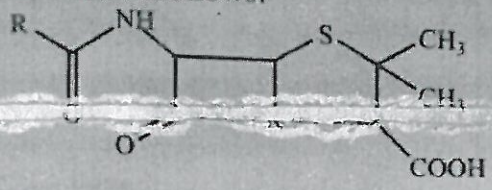
Penicillin acts in the following ways:

1) **Inhibition of Cell Wall Synthesis by Blocking Transpeptidation:** Penicillin acts as an alternative substrate and binds to Penicillin Binding Protein (PBP) receptor present on the surface of bacterial cell wall. PBP is the receptor for substrate peptidoglycan precursor in bacteria. After binding, penicillin inhibits transpeptidase that further inhibits cell wall synthesis.

2) **Activation of Autolytic Enzymes:**
   i) Penicillin activates the autolytic enzymes of bacteria. These enzymes after activation destroy bacteria by creating lesions on them.
   ii) Autolysins, present in bacterial cell wall, maintain the appropriate shape and size of cell and also facilitate cell division. Activity of autolysin is regulated by cell wall and teichoic acid.
   iii) Penicillin destroys the bacterial cell wall and disintegrates teichoic acid, thus activating autolysin and lysing the bacterial cell.

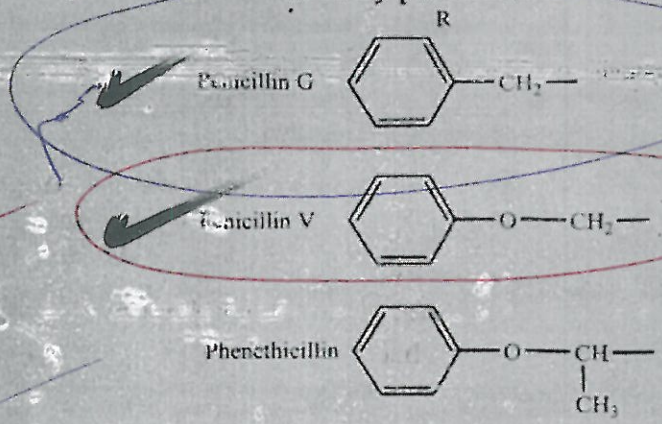
1.2.4.7. Classification

Penicillins are classified as follows:



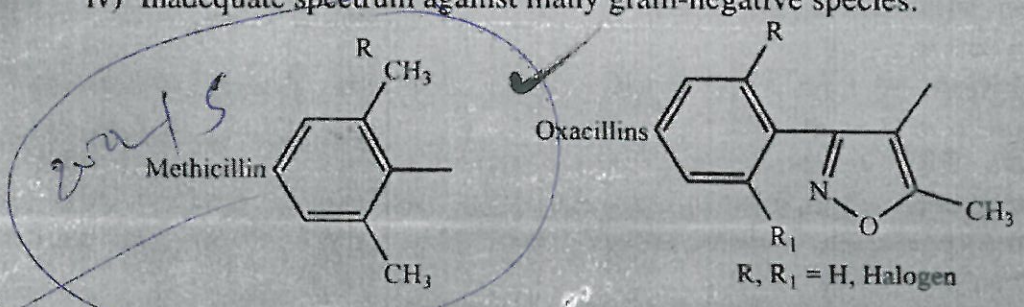
1) Early Penicillins

i) Gram-positive potency against susceptible *Staphylococci* and *Streptococci*.
ii) Active against some gram-positive cocci.
iii) Show good oral absorption but is relatively acid-labile.
iv) Inactive against gram-negative bacilli.
v) Susceptible to deaetivation by penicillinase.



2) Penicillinase-Resistant Penicillins:

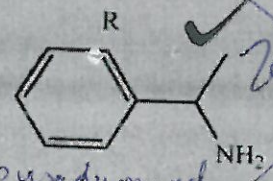
i) Reduced susceptibility to penicillinase.
ii) Active against microorganisms resistant to early penicillins.
iii) Oxacillins show good oral activity.
iv) Inadequate spectrum against many gram-negative species.



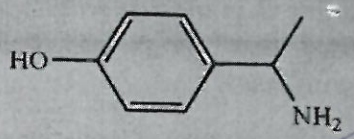
3) Broad-Spectrum Penicillins

i) Shows enhanced spectrum of activity against some gram-negative bacteria.
ii) Retains gram-positive potency.
iii) Shows good oral absorption.
iv) Ampicillin can be given via intravenous and intramuscular route.
v) Amoxycillin is an exceptional oral agent.
vi) Prodrug esters (of ampicillin) enhance the systemic drug levels.
vii) Ineffective against *Pseudomonas aeruginosa*.

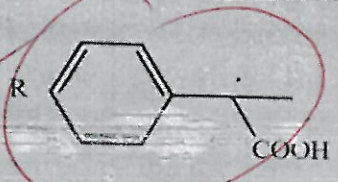
Ampicillin



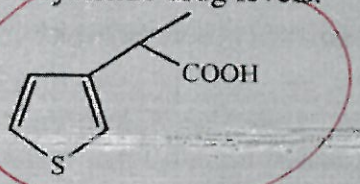
Amoxycillin



i) Shows enhanced spectrum of activity against many pathogenic gram-negative bacteria.
ii) Reduced gram-positive potency.
iii) Active against *P. aeruginosa*.
iv) Shows good oral absorption.
v) Prodrug esters of carbenicillin enhance systemic drug levels.

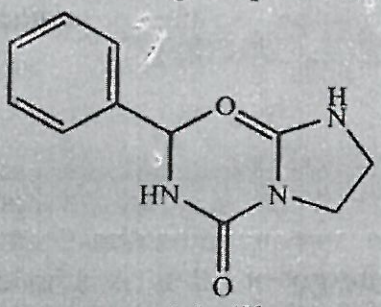


Carbenicillin

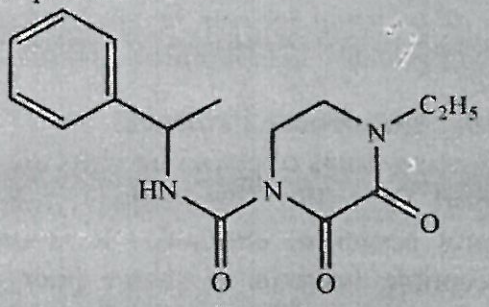


Ticarcillin

5) **Broad-Spectrum Ureido Penicillins**
i) Shows enhanced spectrum of activity against *P. aeruginosa*, expanded activity against *Klebsiella*, *Serratia*, and *Proteus*.
ii) Potent against gram-positive bacteria, but not effective against penicillinase producers.
iii) Exhibits a good pharmacokinetic profile.

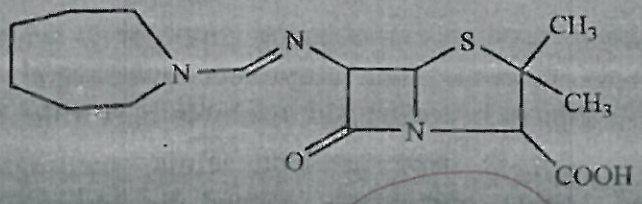


Azlocillin



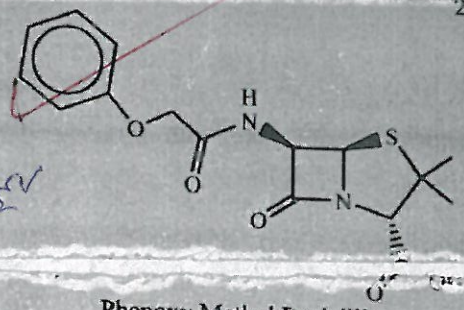
Piperacillin

6) **Penicillin with a C-6 Amidino West-End**
i) Active against *E. coli*, *Klebsiella*, *Shigella*, *Salmonella*, and many other resistant species.
ii) Inactive against *P. aeruginosa*.
iii) Prodrug esters enhance the systemic drug levels.



Mecillinam

2) **Phenoxy Methyl Penicillin (Penicillin V):** Penicillin V is obtained from natural sources. It is better than other penicillin because it is not affected by the action of gastric juices.

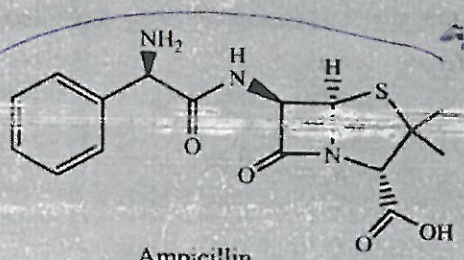


Phenoxy Methyl Penicillin

Properties: Penicillin V exists as a [illegible]. It has a bitter taste and is odourless. It is highly soluble in water; soluble in polar organic solvents; and practically insoluble in vegetable oils and liquid petrolatum.

Uses: Penicillin V is used in mild to moderately severe infections (e.g., dental infection, middle ear infections, rheumatic fever, scarlet fever, heart infections, skin infections, and upper and lower respiratory tract infections).

3) **Ampicillin:** Ampicillin is a broad spectrum penicillin antibiotic of semi-synthetic origin. It is not hydrolysed by various β-lactamases, and it shows bactericidal activity.



Ampicillin

Properties: Ampicillin exists as a white, odourless, crystalline, anhydrous powder. It is soluble in methanol, sparingly soluble in water and ethanol; and insoluble in ether, ethyl acetate, petroleum ether, benzene, and chloroform.

Uses: Ampicillin is used in gastrointestinal infections, respiratory infections, UTIs, and meningitis caused by *E. coli*, *P. mirabilis*, *Enterococci*, *Shigella*, *S. typhosa* and other *Salmonella*, non-penicillinase-producing *N. gonorrhoeae*, *H. influenza*, and *Staphylococci*.

4) **Cloxacillin:** Cloxacillin is a chlorinated derivative of oxacillin and a semi-synthetic antibiotic.

Properties: The sodium salt of cloxacillin exists as a white crystalline hygroscopic powder. It is odourless and very bitter in taste. It is freely soluble in water; highly soluble in cold water; and slightly soluble in chloroform.

Uses: Cloxacillin is used in infections due to penicillinase-producing *Staphylococci*, including *Pneumococci*, penicillin G-sensitive and penicillin G-resistant *Staphylococci*, and group A β-haemolytic *Streptococci*.

5) **Carbenicillin:** Carbenicillin is a semi-synthetic, broad spectrum penicillin. Since it gets affected by gastric juices and penicillinase enzyme, it is administered via parenteral route.

Properties: Carbenicillin exists as a white coloured, water-soluble powder.

Uses: Carbenicillin is used in acute and chronic infections of upper and lower urinary tract, and asymptomatic bacteriuria caused by certain strains of bacteria.