Anti bacterial Drugs

Sulfonamides (Sulpha Drugs)

A considerable progress had been made before 1930 towards the development of externally applicable bactericides, but most bactericides that could be administered internally having reasonably safety margin unfortunately lost their activity in the presence of blood serum. Diseases like pneumonia, meningitis, dysentry etc., could not be treated effectively until the discovery of **sulpha drugs**.The best example of antibacterial agents acting as antimetabolites (Antibacterial agents which act against cell metabolism) are the sulphonamides (sometimes called the sulfa drugs).

The spectrum of action of sulfonamides

It includes mainly the following pathogens:

a) bacteria - pathogenic cocci (Gram-positive and Gram-negative), E. coli, agents of dysentery (Shigella), Vibrio cholerae, agents of gas gangrene (Clostridium), anthrax, diphtheria, catarrhal pneumonia, influenza;

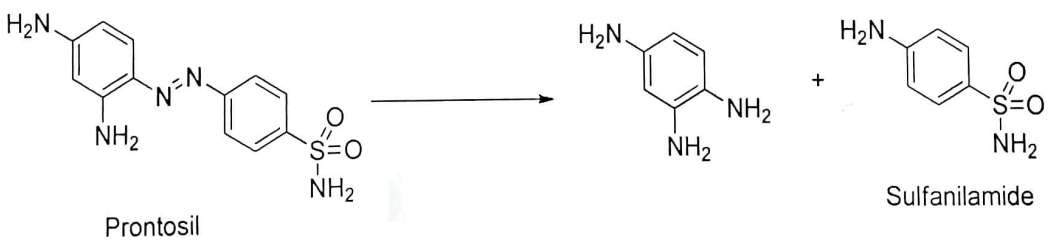
b) Chlamydia - causative agents of trachoma, ornithosis, inguinal lymphogranuloma

c) actinomycetes;

d) the simplest - toxoplasmosis pathogen, Plasmodium malaria.

Particularly active sulfonamides against pneumococci, meningococci, gonococci, some types of hemolytic streptococci, as well as agents of bacillary dysentery.

In 1935 it was discovered that a red dye called prontosil had antibacterial properties in vivo (i.e. when given to laboratory animals). Strangely enough, no antibacterial effect was observed in vitro. In other words, prontosil could not kill bacteria grown in the test tube. This remained a mystery until it was discovered that prontosil was not in fact the antibacterial agent. Instead, it was found that the dye was metabolized by bacteria present in the small intestine of the test animal, and broken down to give a product called sulphanilamide, the compound which was the true antibacterial agent.



Prontosil

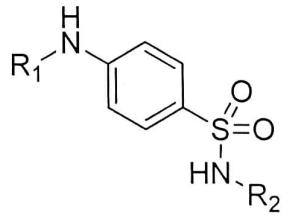
Sulfanilamide

Q. Why Prontosil does not kill bacteria in test tubes but when tested inside animal body it exhibits antibacterial effect? or Prontosil is a prodrug - explain

Thus, prontosil was the first example of a prodrug .Sulfanilamide was synthesized in the laboratory and became the first synthetic antibacterial agent active against a wide range of infections. Further developments led to a range of sulphonamides which proved effective against Gram-positive organisms, especially pneumococci and meningococci.

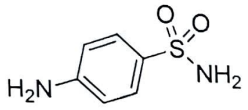
In 1937, two British researchers prepared **'sulphapyridine'** that was indeed the first and foremost structural analogue of **'sulphanilamide'.** This particular compound proved to be a grand and tremendous success in curing pneumonia. This magnificent discovery opened the gateway to the synthesis and screening of hundreds of derivatives of **sulphanilamide,** but only a few have retained the glory of being potent medicinal compounds.

Structure Activity Relationship (SAR)

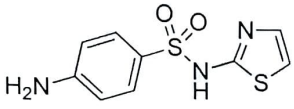


- *P*-amino group is essential for activity and should be free (unsubstituted) except in the case of prodrugs in which it will be as amide linkage that will be hydrolyzed to give the active free form.
- The aromatic ring and the sulfonamide group are important for activity.
- The sulfonamide and the amino group must be directly attached to the ring and in *P* position to each other.
- Any extra substitution will reduce activity.
- Sulfonamide nitrogen must be either primary or secondary

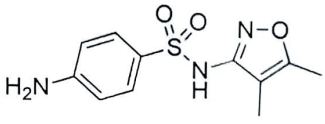
Some important sulphonamides



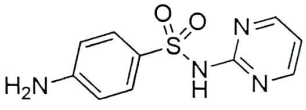
Sulfanilamide pKa = 10.4



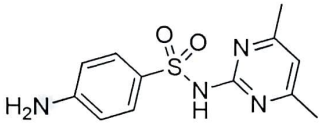
Sulfathiazole pKa = 8.5



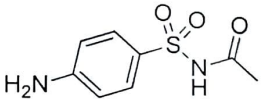
Sulfisoxazole pKa = 5.0



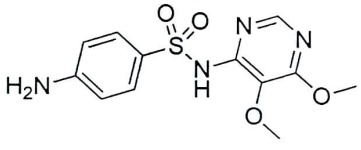
Sulfadiazine pKa = 6.5



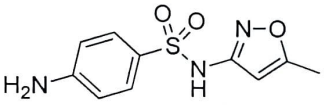
Sulfamethazine pKa = 7.4



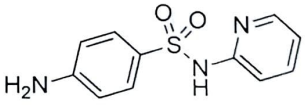
Sulfacetamide pKa = 5.4



Sulfadoxine pKa = 8.1



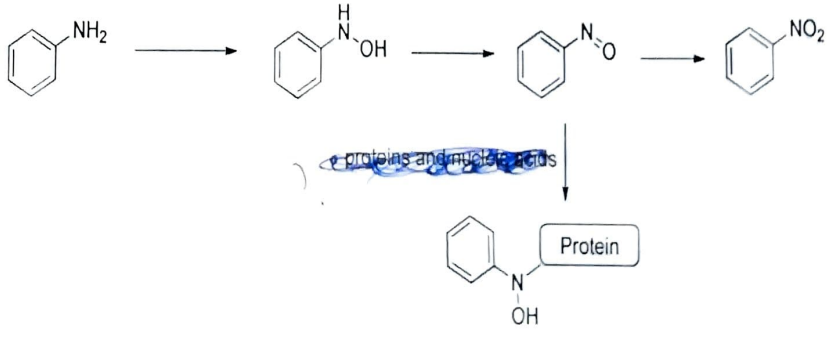
Sulfamethoxazole pKa = 6.1



Sulfapyridine pKa = 8.4

Limitations

Sulfa allergic reactions. The formation of crystalluria. They give toxic metabolites after the oxidation of the aromatic amine



Despite their undoubted benefits, sulfa drugs have proved ineffective against infections such as Salmonella, the organism responsible for typhoid. Other problems have resulted from the way these drugs are metabolized, since toxic products are frequently obtained. For this reason the sulfonamides were mainly being superseded by penicillin.

Classification

Sulphonamides i.e., the systemic antibacterial drugs may be classified broadly on the basis of their site of action as described in the sections that follows :

Sulphonamides for General Infections : These sulphonamides are invariably employed against the streptococcal, meningococcal, gonococcal, staphylococcal and pneumococcal infections. Examples :sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfamerazine, sulfadimidine, sufalene, sulfamethizole etc.

Sulphonamides for Urinary Infections : A number of sulphonamides have been used extensively for the prevention and cure of urinary tract infections over the past few decades. They are used sometiems as a prophylactic before and after manipulations on the urinary tract.

Examples : sulfacetamide, sulfafurazole, sulfisoxazole acetyl, sulfacitine, etc.

Sulphonamides for Local Infection There are some sulphonamides which are used exclusively for certain local applications. Examples :Sulfacetamide sodium, Mafenide, etc.

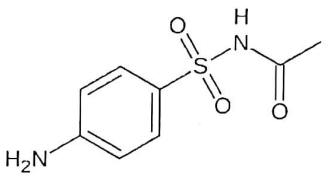
Mode of action of Sulphonamides

Sulfonamides are broad-spectrum, bacteriostatic anti-infectives. They are structural analogs of aminobenzoic acid (PABA) .The sulfonamides act as competitive enzyme inhibitors and block the biosynthesis ofthe vitamin folic acid in bacterial cells. They do this by inhibiting the enzyme responsible for linking together the component parts of folic acid. The consequences of this are disastrous for the cell. Under normal conditions, folic acid is the precursor for tetrahydrofolate-a compound which is crucial to cell biochemistry since it acts as the carrier for one-carbon units, necessary for many biosynthetic pathways. If tetrahydrofolate is no longer synthesized, then any biosynthetic pathway requiring one-carbon fragments is disrupted. The biosynthesis of nucleic acids is particularly disrupted and this leads to the cessation of cell growth and division. Sulfonamides do not actively kill bacterial cells. They do, however, prevent the cells dividing and spreading. This gives the body's own defense systems enough time to gather their resources and wipe out the invader. Antibacterial agents which inhibit cell growth are classed as bacteriostatic, whereas agents which can actively kill bacterial cells (e.g. penicillin) are classed as bactericidal. Sulfonamides act as inhibitors by mimicking p-aminobenzoic acid, one of the normal constituents of folic acid. The sulfonamide

8. Why are sulphonamides act as bacteriostatic agents?

molecule is similar enough in structure to PABA that the enzyme is fooled into accepting it into its active site. Once it is bound, thesulfonamide prevents PABA from binding. As a result, folic acid is no longer synthesized. Since folic acid is essential to cell growth, the cell will stop dividing.

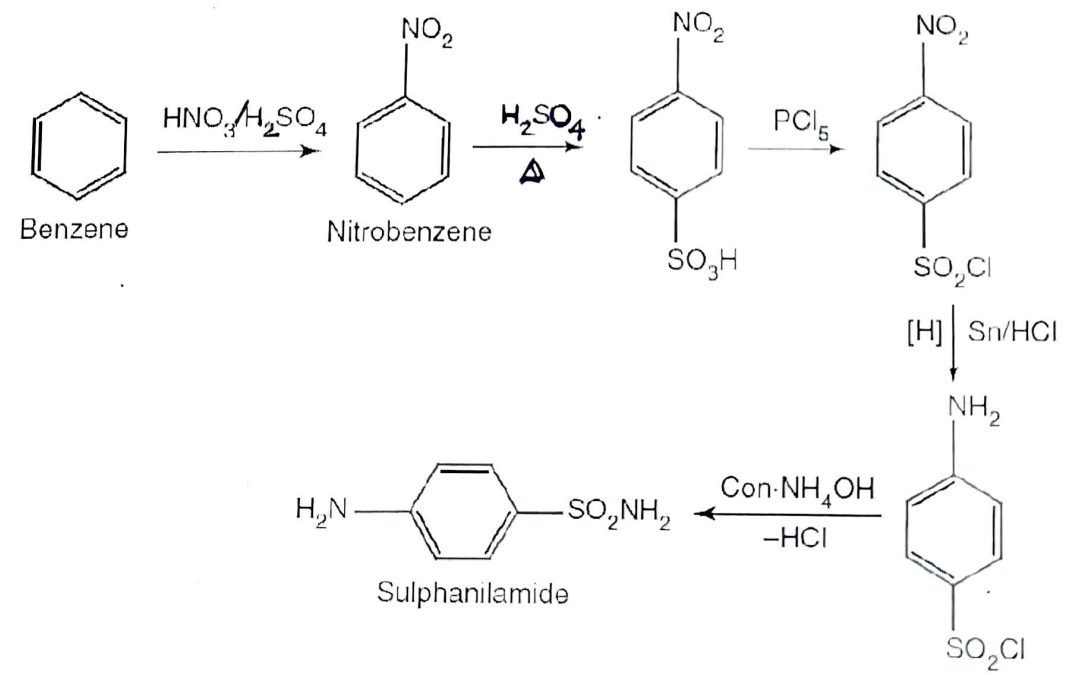
Sulphacetamide

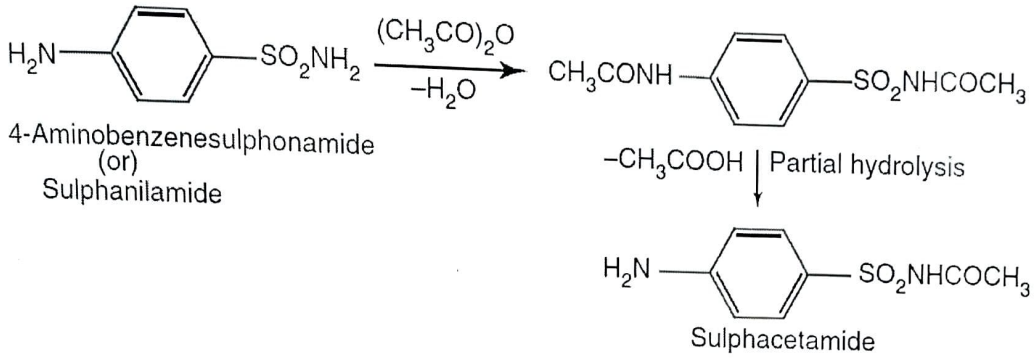


Generic Name: Sulfonamides

Use: The **'drug'** exerts its action topically in conjunction with **sulphabenzamide** and **sulfathiazole** for the control and treatment of vaginitis caused due to the microorganism Gardnerella (Hemophilus) , vaginalis. ~~It has half-life of 7 hours~~.

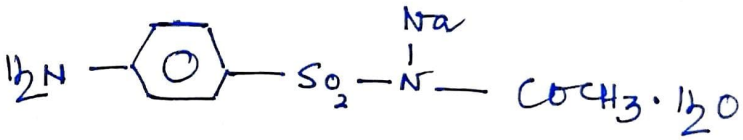
Synthesis: Sulfacetamide is synthesized either by direct alkylation of acetamide with 4-aminobenzenesulfonyl chloride, or by reacting 4-aminobenzenesulfonamide with acetic anhydride and subsequent selective, reductive deacylation of the resultant acetamide using a system of zinc-sodium hydroxide.





Sulphacetamide Sodium

Structure:



It is simply monosodium salt of Suphacetamide

Synthesis:

It may be prepared by heating together **sulfacetamide** and sodium hydroxide in equimolar concentrations.

Use: It is chiefly employed by local application in injuries or infections of the eyes at various strengthsranging from 10 to 30%. It is also used in the treatment of acute conjunctivitis and in the prophylaxis of ocular infections after injuries or burns.

Mode of action:

The **'drug'** is relatively less potent in comparison to **'other sulphonamides'**. This retardation of therapeutic value is perhaps due to the poor penetration into both tissues and bacteria. However, if usedin high concentration by means of local application, it is found to be of great utiliry in different types ofophthalmologic infections, especially those produced by pyogenic cocci, gonococcus, E. coli and Koch-Week's bacillus. As the **'drug'** is obviously nonirritating in nature even at a high dosage regimen, it may be employed safely in sufficient concentration to accomplish adequate penetration of the ocular tissues with much ease and eagerness.

Synthesis :