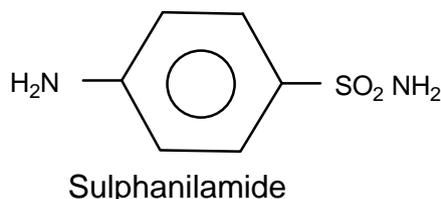


## SULPHONAMIDES

Antibacterial sulphonamides are first effective chemotherapeutic agents used for bacterial infection in humans. The term sulphonamide is usually employed as a generic name for the derivatives of para amino benzene sulphonamides. Sulphonamides inhibit Gram-positive and Gram-negative bacteria, *Nocardia*, *Chlamydia trachomatis* and some *Protozoa*. Some enteric bacteria such as *E.coli*, *Kelbsiella*, *Salmonella*, *Shigella* and *Enterobacter* are inhibited. Sulphonamides are used in the treatment of tonsillitis, septicemia, meningococcal meningitis, bacillary dysentery and number of infections of urinary tract.

Nomenclature of Sulphonamides

Sulphonamides are considered as derivatives of para amino benzene sulphonamide. The nitrogen atom of  $-SO_2NH_2$  is numbered as 1 and the  $-NH_2$  group as 4.



Crystalluria and the pKa

Sulphonamides and their metabolites are excreted almost in the urine. Sulphonamides are not water soluble; they crystallize in the kidney and causes crystalluria. The pKa of sulphamido group of Sulphanilamide is 10.4, that the pH at which 50% of the drug is ionized. Because the urine pH is 6, essentially, all the sulphonamides are unionized and occurs as insoluble form in the kidney. The sulphonamide coming out of solution in urine and kidney causes crystalluria.

Various approaches to adjust the solubility of sulphonamide in urine were performed. They are:

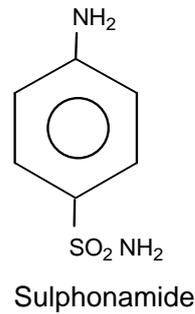
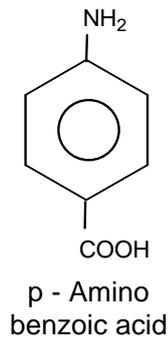
(i) Greatly increasing the urine flow by taking plenty of fluids, so that glomerular filtration rate could be increased, there would be less opportunity to form crystals in renal tubules.

(ii) Increasing the pH of the urine: This is achieved by giving oral sodium bicarbonate before to sulphonamide dose, so that the urine pH will be closure to 10.4.

(iii) Mixed sulphonamides: Mixing different sulphonamide to achieve an appropriate total dose. When several sulphonamides are administered together, the antibacterial activity is the summation of the total sulphonamide concentration present, but the solubility is independent of each other. Thus by giving a mixture of sulphonamide the same therapeutic level can be maintained with much less danger of crystalluria, because only one-third of the amount of any one compound is present. Hence, mixed sulphonamides are in current practice now.

#### Mechanism of Action

Sulphonamides are bacteriostatic in nature. The sulphonamide sensitive micro-organisms require p-Amino benzoic acid (PABA) for the synthesis of folic acid which is essential for the synthesis of DNA and RNA. Sulphonamides block the biosynthesis of this folate coenzyme resulting into the arrest of bacterial growth and cell division.



Sulphonamides may be used systemically, topically or orally for local effects depending upon its solubility. Some uses of sulphonamides are:

- Pneumocystis carinii pneumonia: eg. Trimethoprim and Sulphamethoxazole
- Cerebral toxoplasmosis: eg. Pyrimethamine – Sulphadiazine
- Urinary tract infection: eg. Sulphamethizole
- Nocardiosis: eg. Sulphadiazine, Sulphisoxazole
- Respiratory tract infection: eg. Sulphalene
- Dermatitis herpetiformis: eg. Sulphapyrimidine
- Meningococcal infection: eg. Sulphadiazine
- Burn therapy: eg. Silver sulphadiazine
- Conjunctivitis and Superficial ocular infections: eg. Sulphacetamide
- Traveler's diarrhea (or) GIT infection: eg. Sulphaguanidine
- Chloroquine resistant malaria: eg. Sulphadoxime with Pyrimethamine

- Leprosy: eg. Dapsone

## CLASSIFICATION

Sulphonamide can be classified in various ways

### I. On the basis of site of action

- Sulphonamides for general infections: eg. Sulphanilamide, Sulphapyridine, Sulphadiazine, Sulphamethocine, Sulphamethoxazole.
- Sulphonamides for intestinal infections: eg. Phthalyl sulphathiazole, Succinyl sulphathiazole, Sulphasalazine.
- Sulphonamides for local infections: eg. Sulphacetamide, Mafenamide, Silver sulphadiazine.
- Sulphonamides for dermatitis: eg. Dapsone, Solapsone.
- Sulphonamide Combination: eg. Sulphamethoxazole with Trimethoprim  
 Sulphadiazine with Trimethoprim,  
 Sulphadoxime with  
 Pyrimethamine, Sulphamoxole  
 with Trimethoprim.

### II. On the basis of pharmacokinetic properties

- Poorly absorbed Sulphonamides: (Locally acting sulphonamides)  
 these agents are poorly absorbed in GIT and mainly used to treat intestinal disease or to reduce luminal bacterial population prior to bowel surgery. eg. Sulphasalazine, Phthalyl sulphathiazole.
- Rapidly absorbed and excreted Sulphonamides (Systemic sulphonamides) eg. Sulphamethoxazole, Sulphisoxazole, Sulphadiazine.

iii) Topically used Sulphonamides: They are mainly applied in burns, conjunctival sac, otic canal and vagina to treat bacterial infection.

eg. Mafenide sodium, Sulphacetamide, Silver sulphadiazine.

### III. On the basis of chemical classification

- i)  $N^4$  - substituted Sulphonamides (pro drugs): eg. Prontosil, Sulphaguanidine,
- ii)  $N^1$  - substituted Sulphonamides: eg. Sulphadiazine, Sulphacetamide, Sulphadimidine.
- iii) Both  $N^1$  and  $N^4$  - substituted Sulphonamides: eg. Succinyl sulphathiazole, Phthalyl sulphathiazole.
- iv) Non-aniline Sulphonamides: eg. Mefenide sodium.

### IV. On the basis of pharmacological activity

- i) Antibacterial agents: eg. Sulphadiazine, Sulphisoxazole.
- ii) Oral hypoglycemic agent: eg. Tolbutamide.
- iii) Diuretics: eg. Furosemide, Bumetanide, Chlorthalidone.
- iv) Dermatitis: eg. Dapsone.

### V. On the basis of duration of action

- i) Ultra long acting Sulphonamides: (half life greater than 50 hours)  
eg. Sulphasalazine, Sulphacetamide, Sulphalene.

- ii) Long acting Sulphonamides: (half life greater than 24 hours)  
eg. **Sulphamethoxiazine**,  
Sulphadimethoxine.
- iii) Intermediate acting Sulphonamides: (half life between 10-24 hours)  
eg. **Sulphasomizole**,  
Sulphamethoxazole.
- iv) Short acting Sulphonamides (half life less than 20 hours)  
eg. Sulphamethizole, Sulphisoxazole.

### General Method of Synthesis

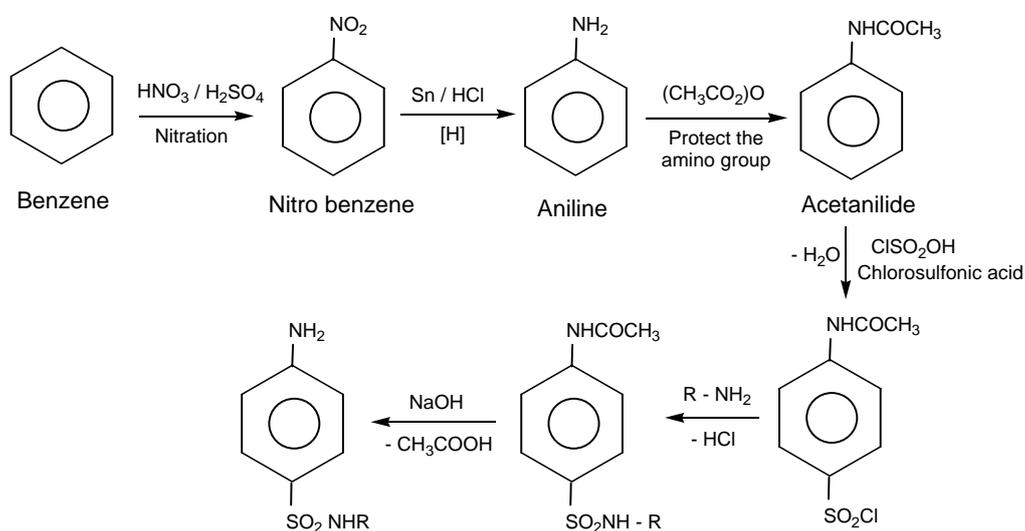
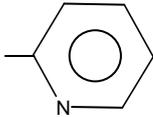
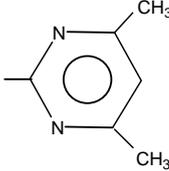
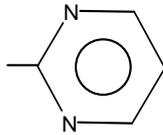
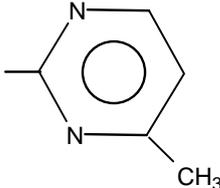
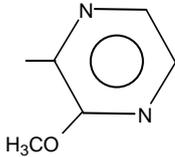
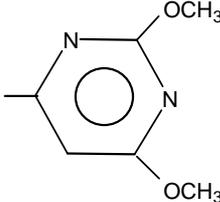
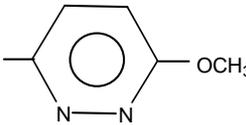
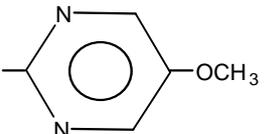
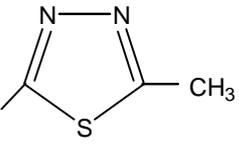
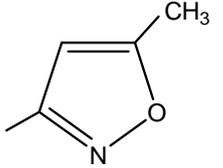
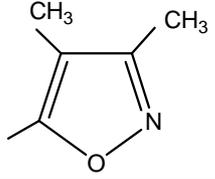
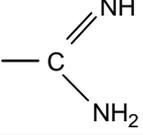
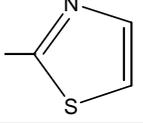
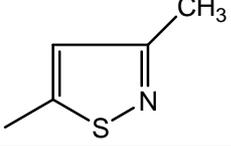
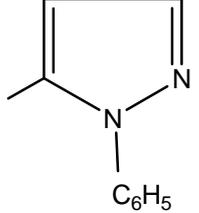
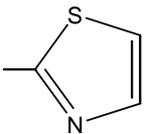
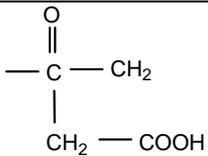
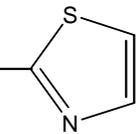
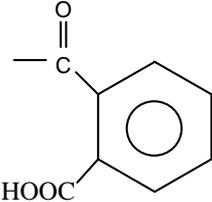


Table: 16.1 Antibacterial Sulphonamides

$\text{R}_1 - \text{NH} - \text{O}_2\text{S} - \text{C}_6\text{H}_4 - \text{NH} - \text{R}_4$ N' - Substituted sulphonamides				
S. No	Generic Name	R <sub>1</sub>	R <sub>4</sub>	Therapeutic uses
1.	Sulphacetamine	- COCH <sub>3</sub>	H	Ophthalmologic use

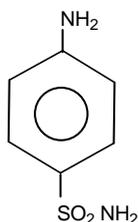
2.	Sulphapyridine		H	Dermatitis herpetiformis
3.	Sulphadimidine		H	Used in meningitis
4.	Sulphadiazine		H	Used in meningitis and nocardiosis
5.	Sulphamerazine		H	Systemic sulphonamide
6.	Sulphalene (Sulphametopyrazine)		H	Chronic bronchitis, respiratory tract infection
7.	Sulphadimethoxine		H	Systemic sulphonamides
8.	Sulphamethoxy - pyridazine		H	Systemic sulphonamides
9.	Sulphamethoxy - diazine		H	Systemic sulphonamides

10.	Sulphamethizole		H	UTI infection
11.	Sulphamethoxazole		H	UTI infection
12.	Sulphisoxazole (Sulphafurazole)		H	Rheumatic fever, UTI infection
13.	Sulphaguanidine		H	Used in GIT infection
14.	Sulphathiazole		H	Systemic sulphonamides
15.	Sulphasoimazole		H	Systemic sulphonamides
16.	Sulphaphenazole		H	Systemic sulphonamides
N <sup>1</sup> and N <sup>4</sup> Substituted Sulphonamides				
17.	Succinyl – sulphathiazole			Intestinal infection

18.	Phthalyl-sulphathiazole			Intestinal infection
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## Sulphonamides for General Infections

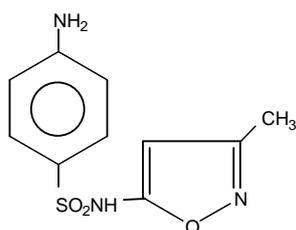
### Sulphanilamide (Prontosil album)



p - Amino benzene sulphonamide

Use: Because of its high toxicity it not in practice now. But still used in veterinary practice as antibacterial agent.

### Sulphamethoxazole (Gantanol)

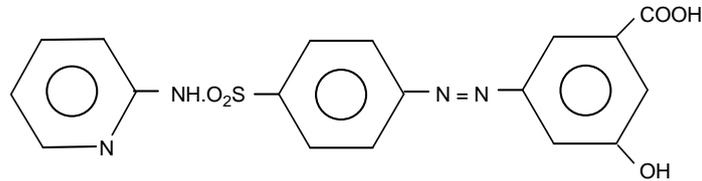


4-Amino-N-(5-methyl -3 - isoxazolyl) benzene sulphonamide

Use: It is used in the treatment of meningitis, lower urinary tract infection caused by *Escherichia coli* and *Proteus mirabilis*.

## Sulphonamides for Intestinal Infections

### Sulphasalazine (Saaz, Salazar)



2- Hydro-5-[[4-(2-pyridinyl amino) sulfonyl] phenyl] azo benzoic acid

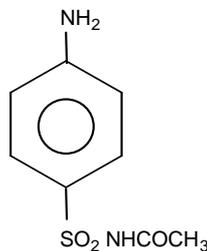
Sulphasalazine is a prodrug, which is cleaved at the N<sup>4</sup> position in the large intestine to m-Amino salicylic acid and Sulphapyridine by azo reductase. Sulphapyridine acts as an antibacterial and amino salicylic acid has an anti-inflammatory effect on the colon. The advantage of this prodrug is the release of amino salicylic acid, which prevents the absorption of the agent (prevents the systemic absorption) so that the duration of action increases (concentrates the drug in the active site). It is mainly used in intestinal infections.

Use: It is used to treat ulcerative colitis and rheumatoid arthritis.

## Sulphonamides for Local Infections

### A. Sulphacetamide (Setride, Zincoren)

Sulphacetamide is a simple acetyl derivative of sulphanilamide, known as Albucid.

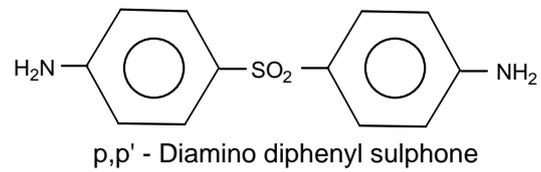


N -sulphanilyl acetamide

Use: Sulphacetamide sodium is used to treat infection or injuries of the eye.

## Sulphonamide for Dermatitis

### Dapsone (DDS)



Used in the treatment of leprosy and nocardiosis.