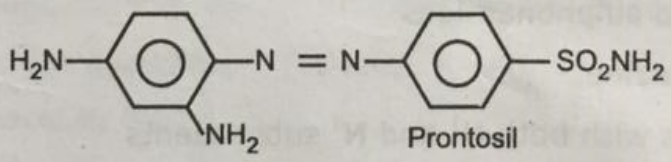
Sulfonamides

Sulphonamides or Sulpha-Drugs

INTRODUCTION

The discovery of sulphonamides as antibacterial agent began early in 1930. **Paul Ehrlich** (1854 - 1915), father of chemotherapy, observed selective staining of microorganisms by dyes. He studied relationship between selective staining and antiprotozoal activity and stimulated the interest in dyes as possible antimicrobial agents.

Later on Horlein and his associates observed that Sulphamoyl ($-SO_2NH_2$) group has affinity for protein molecule. This led to the synthesis of azo-dyes containing $-SO_2NH_2$ group. As a result, diazocompounds containing $-SO_2NH_2$ group were synthesized which also includes prontosil. Though it was synthesized in 1908, its antibacterial activity was identified in 1932 by Gerhard Domagk. In 1935, he declared that Prontosil was effective not because of the presence of azo-group which stains the tissue selectively but because of the p-aminobenzene sulphanilamide, which is obtained by its reductive cleavage in gut. Thus, it is a prodrug and active *in-vivo* and not *in-vitro*. Later on it was shown that small changes in sulphanilamide moiety (e.g. substitution of phenyl ring) abolishes the activity. This led to the conclusion that sulphanilamide is responsible for antibacterial activity. Thus, interest on azo dyes proved to be magic bullet of Ehrlich and focussed the attention on sulphonamides as antibacterial agents.



Prontosil

As it was easy and cheap to prepare sulphonamides, a large number of sulphonamides are synthesized. About 40 sulphonamides are in clinical practice and only sulphamethoxazole appears in top 100 drugs. These sulpha drugs are still widely used in developing countries as they can be stored in adverse conditions unlike penicillin.

Classification :

Chemotherapeutic agents that contain $-SO_2NH_2$ (sulphamoyl) group, can be placed into two groups :

(A) Synthetic antibacterial sulphonamides which are called as sulpha drugs :

(B) Non-anti-bacterial sulphonamides, e.g.

(a) Diuretics - frusemide, chlorothiazide, hydrochlorthiazide

(b) Hypoglycemic agents.

e.g. chlorpropamide, tolbutamide.

1. The synthetic antibacterial sulphonamides can be grouped as follows :

(i) Sulphanilamide (aniline substituted) derivatives.

e.g. sulphadiazine, sulphaguanidine.

(ii) Prodrugs that produce sulphanilamide *in-vivo*.

e.g. sulphasalazine.

(iii) Non-anilides (non-aniline) sulphonamides.

e.g. mefenide.

2. Chemical classification :

(i) N^1 - substituted sulphonamides

(a) with acyclic substituents

e.g. sulphacetamide, sulphaguanidine

(b) with heterocyclic substituents

e.g. sulphadiazine, sulphamethoxazole, sulphadimethoxine, sulphamethoxypyridazine.

(ii) N_4 - substituted sulphonamides

e.g. sulphasalazine.

(iii) Sulphonamides with both N^1 and N^4 substituents

e.g. phthalylsulphathiazole, succinylsulphathiazole.

3. Classification based on absorption and half-life (t/2)

(A) On the basis of absorption :

1. Sulphonamides which are poorly absorbed orally and are used for intestinal infections.
2. Absorbable compounds for systemic use.

(B) On the basis of duration of action, the sulphonamides are classified as :

(i) Short-acting sulphonamide (plasma half-life less than 10 hours)

(a) poorly absorbed and locally acting.

e.g. sulphaguanidine, phthalyl sulphathiazole, succinyl sulphathiazole.

(b) absorbed and excreted rapidly.

e.g. sulphacetamide.

(ii) Medium-acting sulphonamides (plasma half life is between 10–24 hours)

e.g. Sulphamethoxazole, sulphadiazine.

(iii) Long-acting sulphonamides (plasma half life is more than 24 hours)

e.g. Sulphadimethoxine, Sulphamethoxypyridazine.

(iv) Ultra-long acting sulphonamide : **Sulphamethoxine**, Sulphamethoxypyrazine having half life of about 150 hrs. and 65 hrs. respectively.

4. Classification depending upon their therapeutic uses :

(a) Sulphonamides are used for systemic infections :

(i) Those used in urinary tract infections

e.g. Sulphamethoxazole, Sulphacetamide.

(ii) Those used in respiratory tract infections

e.g. Cotrimoxazole, Sulphadiazine.

(iii) Those used in meningeal infections

e.g. Sulphadiazine.

(b) Sulphonamides are used for local infections :

(i) Those used for intestinal infections.

e.g. Sulphaguanidine, Phthalylsulphathiazole, Succinyl sulphathiazole.

(ii) Those used for opthalmic infections.

e.g. Sulphacetamide.

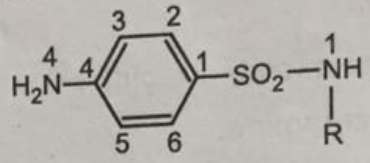
(iii) Those used in burn therapy.

e.g. Mefenide, Silver sulphadiazine.

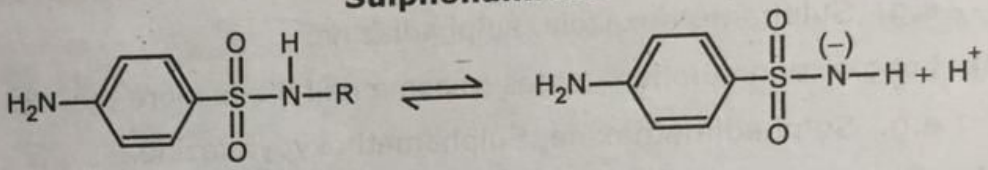
(A) CHEMISTRY AND NOMENCLATURE OF SULPHA-DRUGS

The general term 'Sulpha' drugs or 'Sulphonamides' has been used for antimicrobial (antibacterial) agents. It is restricted to N-substituted derivatives of the parent substance, sulphanilamide (p-amino benzene sulphonamide), in which one hydrogen atom of sulphamoyl group ($-SO_2NH_2$) is replaced by various substituents.

The other –H atom is sufficiently acidic to form stable salts. The nitrogen of sulphamoyl (sulphonamido) group is called N^1-nitrogen and nitrogen at C_4 is called as N^4 nitrogen. Hence, the substituents present at N^1 and N^4 nitrogens are called N^1-substituents and N^4-substituents respectively. The single pK_a usually given by sulphonamides is due to loss of H^+ ion from sulphamoyl nitrogen.



Sulphonamides



The minus charge on nitrogen atom is normally not very stable but in sulphonamides, it is stabilised by resonance (delocalisation). The pK_a of sulphanilamide is 10.4. At urine pH (pH = 6), sulphanilamide is very slightly soluble in water and is in unionised form. It is metabolised in body to N^4-acetyl derivative which is still less soluble than sulphanilamide and thus frequent administration causes crystalluria. Sulphanilamide is water soluble above pH 10. In order to get sulphonamides having lower pK_a, closer to urine pH, different N^1–monosubstituted derivatives are synthesized. The different electron withdrawing substituents are acetyl, guanidyl or heterocyclic groups. Due to this, the drugs are about 50% ionised at urine pH and antibacterial activity is increased. These drugs penetrate bacterial cell wall in unionised form and after penetration they get ionised and act as antibacterial. The structure of sulphanilamide closely resembles (is bio-isostere of) p-amino-benzoic acid (PABA), a growth factor for bacteria. Thus, sulphonamides are competitive inhibitors of PABA and so prevent normal utilisation of PABA for synthesis of folic acid. Free p-amino group is essential for antibacterial activity. Hence, N^4 -substituents which are not removed *in-vivo*, will result in loss of activity of sulpha drugs.

The generic name of sulpha drug is built up by adding prefix 'sulpha' to the abbreviated chemical name of N^1-substituent. The N^4-substituent is prefixed to 'sulpha'. Thus, in succinyl sulphathiazole, thiazole is N^1-substituent and succinyl group is N^4-substituent.

(B) PHYSICAL PROPERTIES OF SULPHA DRUGS

They are white or yellowish white crystalline powder, odourless and very slightly soluble in water but soluble in aqueous alkali hydroxide solution and dilute mineral acids.

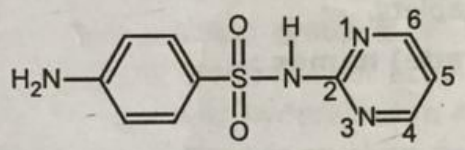
Taste :

(a) tasteless. e.g. sulphadiazine, sulphaguanidine, sulphadimethoxine.
(b) acidic and saline taste. e.g. sulphacetamide.
(c) slightly bitter taste. e.g. phthalylsulphathiazole, succinylsulphathiazole, sulphamethoxypyridazine.
(d) bitter after taste - sulphamethoxazole.

(C) STABILITY AND STORAGE OF SULPHA DRUGS

They are affected by heat and light and the presence of air and moisture accelerates the effect. Hence, they are stored in tightly-closed, light-resistant containers.

1. SULPHADIAZINE



2 - (p-aminobenzene sulphonamido) pyrimidine

OR

2 - sulphanilamido pyrimidine

OR

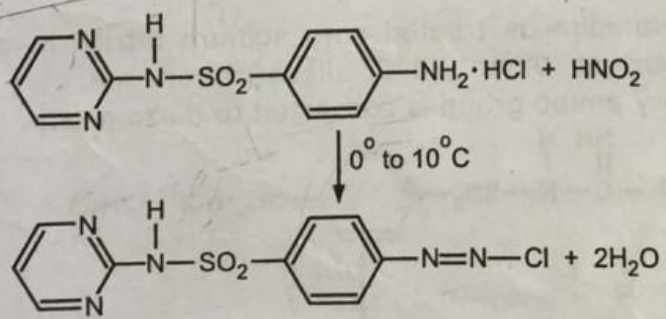
N^1-(pyrimidin - 2 - yl) sulphanilamide.

Chemical Properties :

1. **Diazotisation reaction :** When sulphadiazine is treated with sodium nitrite in presence of conc. hydrochloric acid at 0° to 10°C, it undergoes diazotisation giving diazo compound.

(a) $NaNO_2 + HCl \longrightarrow NaCl + HNO_2$

(b)



p-(pyrimid–2 –yl amino sulphonyl) benzene diazonium chloride.

This reaction is used for its assay.

2. When sulphadiazine is dissolved in 0.1 N sodium hydroxide and to this 1% copper sulphate solution is added, purple brown coloured ppt. is obtained. This is the test for its identification.

Uses :

1. It has an antibacterial activity, hence it is used in the treatment of :
   (i) Meningitis (as it can penetrate the blood brain barrier)
   (ii) Urinary tract infections.
   (iii) Toxoplasmosis in combination with pyrimethanamine.
2. Its silver salt, silver sulphadiazine, is used topically in the treatment of burn therapy.

Pharmaceutical preparations :

1. Sulphadiazine tablets.
2. Sulphadiazine injection or sulphadiazine sodium injection.
3. Trisulphapyrimidine tablets.

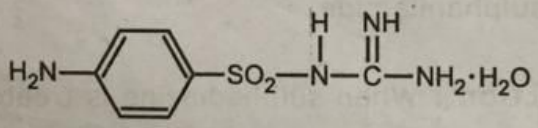
Proprietary (or brand or trade) names :

Atrina, Cotrizine, Trimozin.

Note : Sulphadiazine is also given in conjunction with trimethoprim. This combination is named as co-trimazine. It has similar actions and uses to co-trimoxazole.

2. SULPHAGUANIDINE

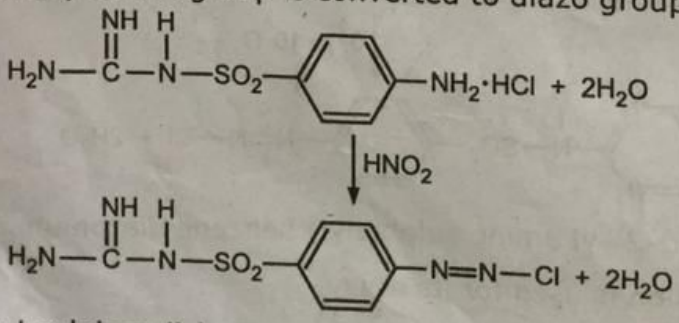
Structure :



Chemical name : N-(p-aminobenzene sulphonyl) guanine monohydrate OR 1-(4-aminobenzene sulphonyl) guanidine monohydrate OR 1-sulphanimyl guanidine monohydrate OR N^1 - amidino sulphanilamide monohydrate.

Chemical Properties :

1. When sulphaguanidine is treated with sodium nitrite in presence of conc. hydrochloric acid at 0° to 10°C, diazotisation reaction occurs in which aromatic primary amino group is converted to diazo group.



p-(guanidinyl sulphonyl) benzene diazonium chloride.

2. As under sulphadiazine (chemical property no. 2) it gives blue coloured precipitate.

   This is a test for identification.

Uses :

It is antibacterial and is poorly absorbed through (is retained in) gastro-intestinal tract. Hence, it is used in the treatment of local intestinal infections like bacillary dysentery.

Pharmaceutical preparations :

1. Sulphaguanidine tablets

Brand names : Ganidan, Guanimycin, Entrogen.

3. PHTHALYLSULPHATHIAZOLE

In this, –H atom of sulphamoyl nitrogen is replaced by 2-thiazolyl heterocycle and the –H atom of aromatic amino group is replaced by phthalyl group. Thus, 2-thiazolyl heterocycle is N^1-substituent and phthalyl group is N^4–substituent. Introduction of N^1 heterocycle substituent improves anti-bacterial activity. N^4–substituent prevents absorption through G.I. tract. It is slowly hydrolysed in intestine and hence is useful in local intestinal infections. It is preferred to sulphaguanidine as antibacterial in the ulcerative colitis (ulceration of the intestinal mucosa), because in such condition, sulphaguanidine is absorbed into blood stream in dangerous amounts but phthalylsulphathiazole is poorly absorbed.

Chemical properties :

(i) Aromatic amino group is substituted and hence the compound is hydrolysed by boiling with sodium hydroxide to get primary aromatic amino group and then the diazotisation reaction is done as discussed in sulphadiazine.

(ii) Refer chemical property no. 2 under sulphadiazine → green coloured precipitate is obtained.

(iii) When phthalylsulphathiazole is heated for 1 minute with resorcinol and conc. sulphuric acid and the mixture is poured in aq. NaOH solution, a distinct green fluorescence is produced which disappears when the solution is acidified.

Uses :

It is antibacterial and is not absorbed through G.I. tract. Hence, it is used :

(i) in the treatment of bacillary (bacterial) dysentery.

(ii) to reduce bacterial flora of the large intestine before surgery.

Pharmaceutical preparations :

1. Phthalylsulphathiazole tablets.

Brand Names : Colicitina, Talidine.

4. SUCCINYLSULPHATHIAZOLE

It differs from phthalylsulphathiazole, in having N_4-succinyl (– CO – CH_2 – CH_2 – COOH) group instead of N^4 – phthalyl group.

Uses :

As under phthalylsulphathiazole.

Pharmaceutical preparations :

1. Succinylsulphathiazole tablets.
   Brand names : SS Thiazole, Cremomycin, Cremostep, Sulphamycin.

5. SULPHADIMETHOXINE

In this, –H of sulphamoyl group is replaced by 2, 6-dimethoxy pyrimidin-4-yl heterocycle.

Chemical properties :

1. Due to presence of free primary aromatic amino group, it gives diazotisation reaction, described under sulphadiazine.
2. Refer chemical property no. 2 under sulphadiazine, gives yellowish green precipitate.

Uses :

It is a long acting antibacterial agent and is used in the treatment of urinary tract infections.

Pharmaceutical preparations :

1. Sulphadimethoxine tablets
   Brand names : Bensulfa, Sulfadren, K-Prim.

6. SULPHAMETHOXYPYRIDAZINE

In this, the substituent present at sulphamoyl nitrogen is 6-methoxy-pyridazin-3-yl.

Chemical properties :

1. See chemical property no. 1 as under sulphadimethoxine.
2. Refer chemical property no. 2 as under sulphadiazine, gives greenish brown precipitate.

Uses :

As under sulphadimethoxine.

Pharmaceutical preparations :

1. Sulphamethoxypyridazine tablets.
   Brand names : Dyrasul, Confin.

7. COTRIMOXAZOLE

It is a mixture of 5 parts of sulphamethoxazole and 1 part of trimethoprim.

Sulphamethoxazole is a sulphanilamide derivative in which one – H atom of sulphamoyl group is replaced by 5-methyl isoxazol-3-yl heterocycle. Presence of heterocyclic ring improves antibacterial activity. It has pK_a 5.6 (25°C). It is white crystalline powder, odourless and has bitter after-taste. It is very slightly soluble in water.

Trimethprim is a pyrimidine derivative in which two amino groups are present at 2 and 4 positions and 3, 4, 5-trimethoxy benzyl group at C_5. The presence of methoxy groups in phenyl nucleus reduces the lipophilicity and thus optimum activity is obtained. It is not only antimalarial but also has antibacterial activity.

It is white to yellowish powder, odourless and has very bitter taste. It is very slightly soluble in water.

When sulphamethoxazole is given alone, a resistance develops to susceptible bacteria and needed higher dose and also produces toxic effect like crystaluria. Trimethoprim also develops resistance when given alone. When combination of these two drugs of similar pharmacokinetic properties are administered, the spectrum of antimicrobial activity increases. This is due to the synergistic effect arising from 'sequential inhibition' of both dihydrofolate synthatase and dihydrofolate reductase (thus prevent formation of tetrahydrofolic acid). Also, the resistance is not easily developed.

This combination is used in the treatment of :

(i) genito-urinary tract infections,
(ii) respiratory tract infections like bronchitis and pneumonia,
(iii) meningitis (due to meningococcal infections),
(iv) enteric infections (like typhoid and paratyphoid).

Pharmaceutical preparations :

(a) Sulphamethoxazole :

(i) Sulphamethoxazole tablets
(ii) Sulphamethoxazole oral suspension

(b) Cotrimoxazole :

(i) Cotrimoxazole tablets
(ii) Cotrimoxazole injection
(iii) Dispersible cotrimoxazole tablets
(iv) Paediatric cotrimoxazole tablets
(v) Paediatric cotrimoxazole mixture.

(c) Trimethoprim and sulphadiazine :

(i) Trimethoprim and sulphadiazine tablets
(ii) Trimethoprim and suphadiazine injection
(iii) Trimethoprim and sulphadiazine mixture
(iv) Trimethoprim and sulphadiazine dispersible powder.

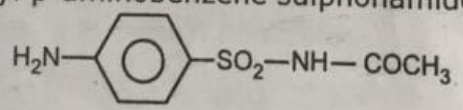
(d) Trimethoprim and sulphadoxine :

(i) Trimethoprim and sulphadoxine tablets
(ii) Trimethoprim and sulphadoxine injection.

Brand names : (i) Bactrim (ii) Septran, (iii) Ciplin, (iv) Uritrim.

8. SULPHACETAMIDE

It is N^1-acetyl derivative of p-aminobenzene sulphonamide (sulphanilamide). Chemical name - N^1 - acetyl p-aminobenzene sulphonamide structure :



It is official in L.P. as its sodium salt.

Chemical properties :

(i) It undergoes diazotisation reaction (refer sulphadiazine)

(ii) Refer chemical property number 2 as under sulphadiazine, gives blue coloured ppt.

Uses :

It is an antibacterial. Hence, it is used :

(i) Locally, to treat eye infections

(ii) Systemically, to treat urinary tract infections.

Pharmaceutical preparations :

(i) Sulphacetamide eye drops.

(ii) Sulphacetamide eye ointment.

Brand names : Albucid, Locula, Ne-Ba-Sulf, Eycula.

QUESTIONS

1. How were sulphonamides introduced in clinical practice ? [2]
2. Classify sulphonamides on the basis of absorption and half-life period giving suitable examples. [3]
3. Classify sulphonamides depending upon their therapeutic uses, giving suitable examples. [3]
4. Describe chemistry and nomenclature of sulphonamides. [4]
5. Write structure, give chemical name, physical properties, one chemical property and uses of sulphadiazine or sulphaguanidine. [4]
6. Explain : **[2 marks each]**
   (i) Phthalylsulphathiazole is preferred to sulphaguanidine in ulcerative colitis.
   (ii) Combination of sulphamethoxazole and trimethoprim is preferred to individual drugs.
   (iii) Succinylsulphathiazole is useful in intestinal infections.
7. Write a short note on co-trimoxazole. [4]
8. Give one test to distinguish sulphadiazine, sulphacetamide and phthalylsulphathiazole. [2]
9. Mention official preparations of any three of the following : **[1 mark each]**
   (i) Cotrimoxazole
   (ii) Sulphacetamide
   (iii) Sulphadiazine
   (iv) Trimethoprim.
10. Mention uses of : **[1 mark each]**
    (i) Sulphadiazine
    (ii) Cotrimoxazole
    (iii) Sulphacetamide
    (iv) Phthalylsulphathiazole.