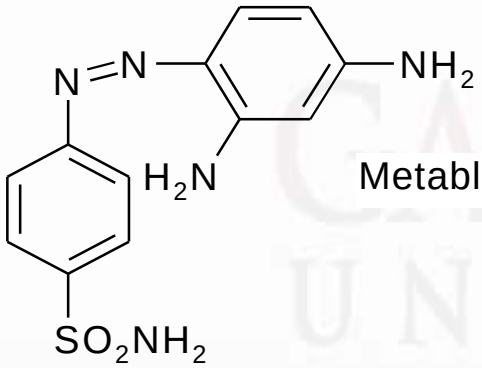
SULPHONAMIDES

Description

- One of the oldest antibacterial agents used to combat infection
- Used for coccal infection in 1935
- They are bacteriostatic because it inhibits bacterial synthesis of folic acid
- Clinical usefulness has decreased because of the effectiveness of other antibiotics and penicillin

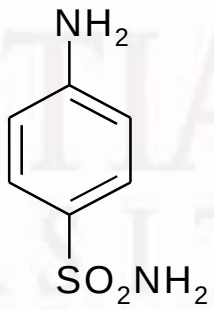
- Presence of free amino group

- Prontosil red → Prodrug
- In vitro ⟹ Inactive
- In vivo ⟹ Active



Prontosil Red

Metablic cleavage



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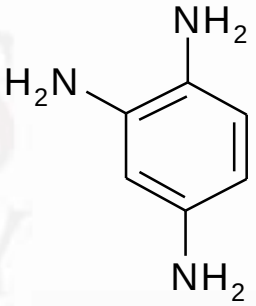
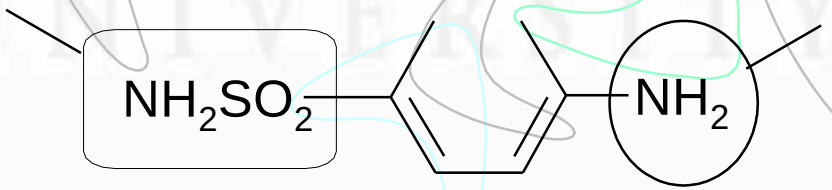


Sulphonamide

- Chemical modification of the sulphonamide structure has given rise to several important group of drugs.
  - Gloucoma – Acetazolamide
  - Diuretic – Thiazides
  - Anti-mycobacterial – Sulphones
  - Oral hypoglycemic – Sulphonyl ureas

- 1) Sodium salt-- water soluble
2)Substitution on these group gives different molecules having different pharmacokinetic properties

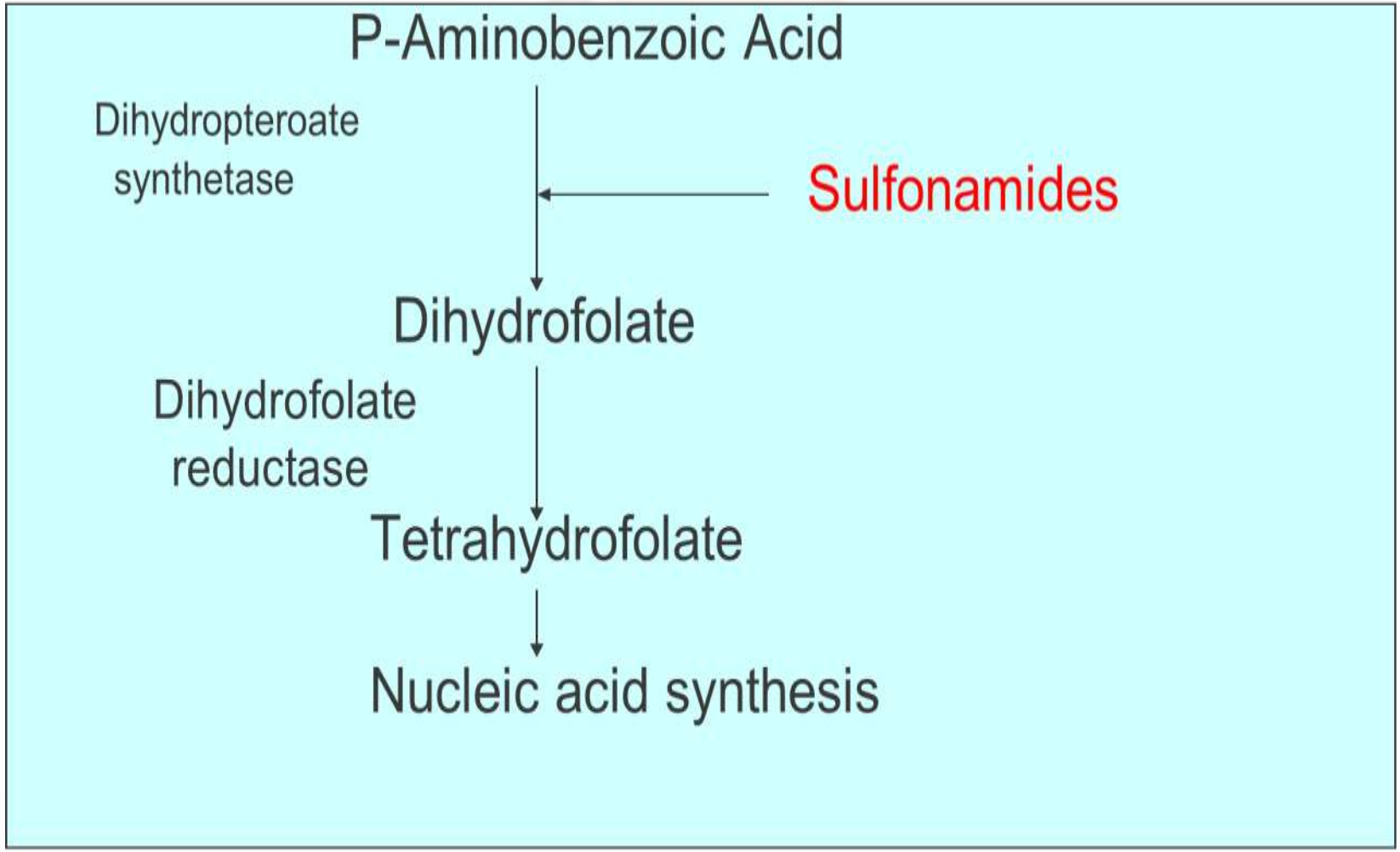


- Substitution gives prodrug

Mechanism of action

- Competitive inhibitor to dihydropteroate synthase enzyme due to resemblance with para-amino benzoic acid.
- Sulfonamides therefore are reversible inhibitors of folic acid synthesis and bacteriostatic not bactericidal.
- Inhibit bacterial growth without affecting normal cells

MECHANISM OF ACTION



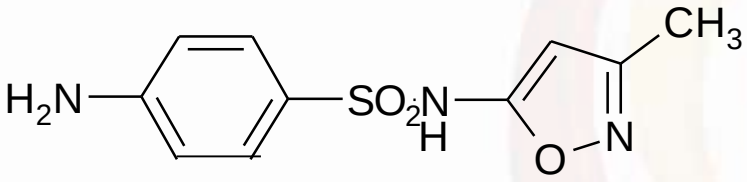
Antibacterial activity

- Gram-positive and gram negative.
- Nocardia, chlamydia trachomatis, some protozoa.

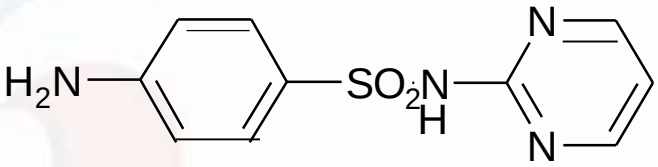
Classification

A. Sulphonamides employed for treatment of systemic infection. Depending upon duration , they can be further subdivided into

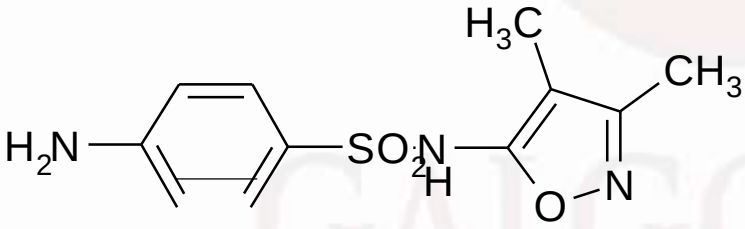
a) Short to intermediate acting sulphonamides.



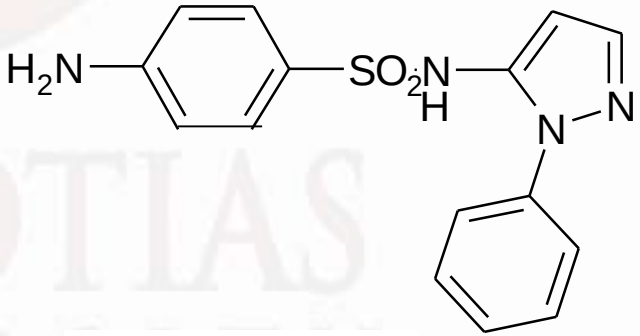
Sulphamethoxazole



Sulphadiazine

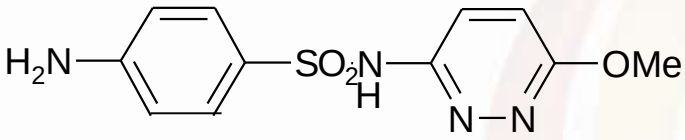


Slpfisoxazole

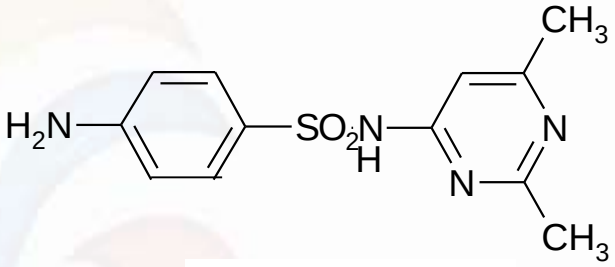


Sulphaphenazole

B. Long acting sulphonamides

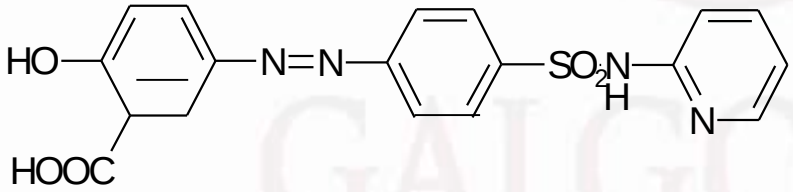


Sulphamethoxypyridazine

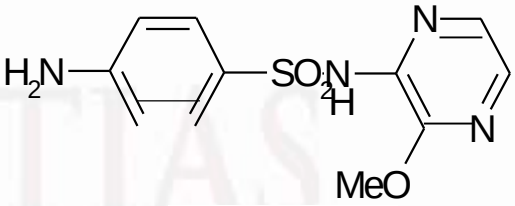


Sulphadimethoxine

C. Extra long acting sulphonamides

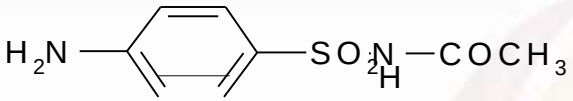


Sulphasalazine

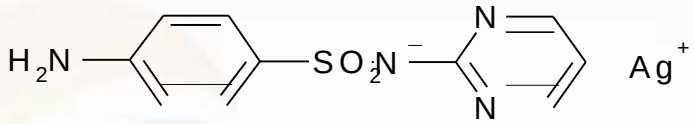


Sulphadiazine

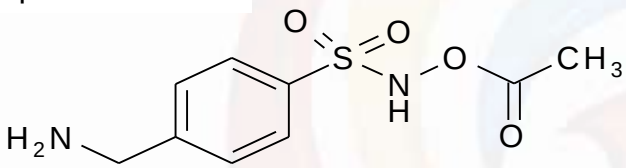
2. Poorly absorbed sulphonamides



Sulphacetamide

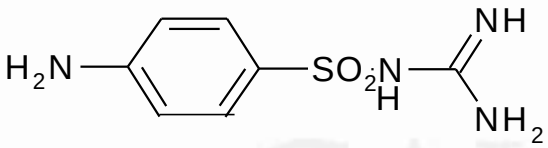


Silver Sulphadiazine

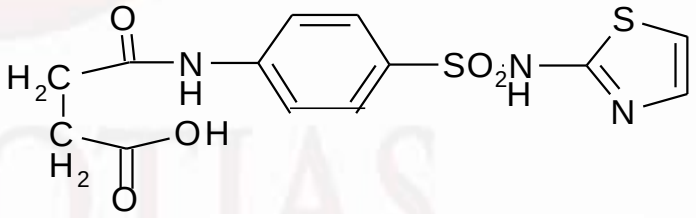


Mafenide acetate

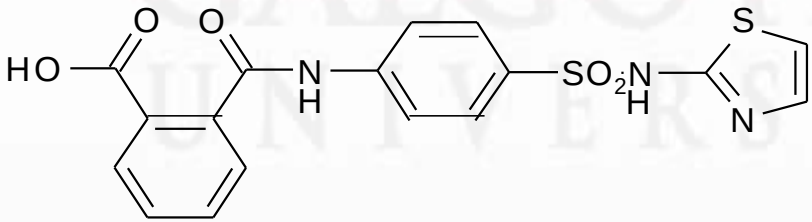
3. Topically used sulphonamides



Sulphaguanidine



Succinyl Sulphathiazole



Phthalyl Sulphathiazole

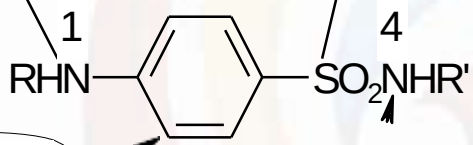
STRUCTURE ACTIVITY RELATIONSHIP

- General

1. Sulphonamide skeleton is the minimum structural requirement for antibacterial activity.
2. The active form of sulphonamide is the ionized form. Maximum activity is observed bretween the pk_a value 6.6-7.4.
3. Sulphonamides competes for binding site on plasma albumin with causes increased action of drugs like

The free aromatic amino group should reside para to the sulphonamide group

Sulphur atom should be directly linked to the benzene ring



Substituents at these positions results in devoid of antibacterial activity

Substitution at this position activity varies with the nature of substituents.

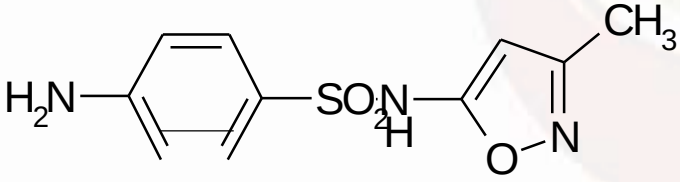
1) Electron donating substituents to SO2 leads to increase in antibacterial activity.
2) Heterocyclic substituents leads to highly potent derivatives.
3) ubstitution of free Sulphonic acid (-SO3H) group for sulphonamide function destroys activity.
4)Replacement by a sulfinic acid group (-SO2H) an acetylation of N1 positio retains activity.

Structure activity relationship of sulphonamide

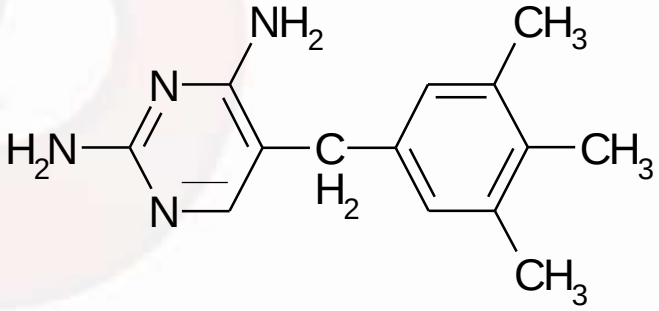
Therapeutic uses

- Urinary tract infections
- Upper respiratory tract infections
- Nocardiosis
- Sulfasalazine in IBD.
- Sulfacetamide in bacterial conjunctivitis & trachoma
- Silver sulfadiazine for prevention of infection of burn wounds .

Trimethoprim - Sulfamethoxazole combination (Co-trimoxazole)



Sulphamethoxazole



Trimethoprim

Mechanism of action:

- Sequential blocking of purine synthesis (synergism).
- Trimethoprim inhibits dihydrofolate reductase enzyme so inhibits tetrahydrofolic acid synthesis
- The combination is bactericidal

Clinical uses

- Acute or Complicated or recurrent urinary tract infections especially in females
- Upper respiratory tract infections
- Pneumocystis jiroveci pneumonia
- Toxoplasmosis
- Shigellosis
- Nocardiosis

Clinical uses continues……

- Typhoid fever
- Salmonella infections
- Prostatitis
- Community –acquried bacterial pneumonia

Reference

- William O. Foye.,Textbook of Medicinal Chemistry, Pg. no: 1089 -1106
- Sriram., Medicinal Chemistry, Pg. no: 295-309.
- Kadam., Textbook of Medicinal Chemistry, Pg. no: 68-82.
- Ilango., Principles of Medicinal chemistry(vol.1), Pg. no: 121-143.
- Good man And GilMan's; The Pharmacology Basis Of Therapeutics Tenth Edition, pg. no 1189-1225.
- JH Block & JM Beale., Wilson & Giswold's Textbook of Organic Medicinal Chemistry & pharmaceutical chemistry 12th Edition, 2011, pg. No. 260-294.