Chapter 15: Sulphonamides and Sulfones

Sulphonamides and Sulfones

Historical development, chemistry, classification and SAR of Sulfonamides: Sulphamethizole, Sulfisoxazole, Sulphamethizine, Sulfacetamide*, Sulphapyridine, Sulfamethoxaole*, Sulphadiazine, Mefenide acetate, Sulfasalazine.

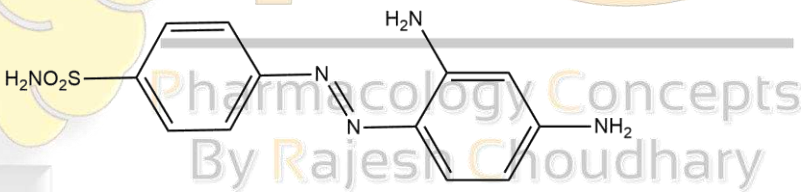
Folate reductase inhibitors: Trimethoprim*, Cotrimoxazole.

Sulfones: Dapsone*.

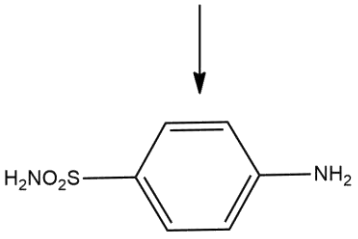
15.1. SULPHONAMIDES

15.1.1. Historical Development

- Sulfonamide was firstly noted as anti-bacterial in 1900's by **Gerhard Domagk**; a Nobel Prize winner in 1939.
- In his attempt to save his daughter from streptococci killing infection, he observed that prontosil; a sulfonamide dye, can selectively restrain the infectious bacteria cells.



Prontocil



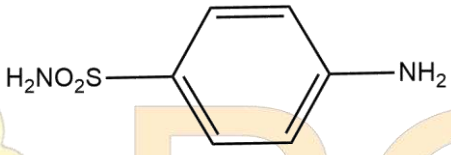
Sulfanilamide

- In 1936, Ernest Fourneau found out prontosil pathway in human body. He discovered that this dye was a pro-drug. It, changes in human body to sulfanilamide which is the anti-bacterial active agent.

- This invention triggered the discoveries of other anti-bacterial members derived from this chemical group such as **sulfapyridine in 1938 against pneumonia**, and **sulfacetamide in 1941 against urinary tract infections**, and **succinoylsulfathiazole in 1942 against gastrointestinal tract infections**

15.1.2. Chemistry

- Chemically sulfa drugs are amphoteric. They behave as **weak organic acid** with pKa 4.79 to 8.56.
- Though they are weakly soluble in water, their solubility is increased at alkaline pH. Sodium salts are however easily soluble in water.
- The **sulfacetamide** is neutral in pH and is used to combat eye infections.

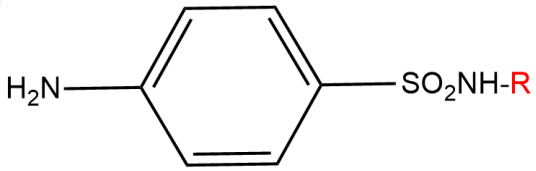


Sulfanilamide

4-aminobenzenesulfonamide

- The Nitrogen of amino group at para position is designated as N^4 while nitrogen of SO2NH2 is designated as N1. Systemic Sulfa drugs are produced by substitution at N1 position whereas gut active sulfa drug are produced by substitution N4 position.

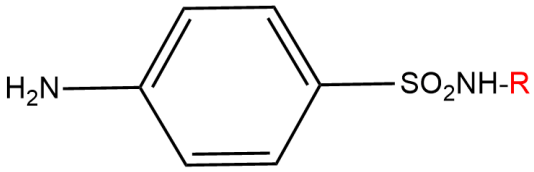
15.1.3. SAR of Sulphonamide



The major features of SAR of sulphonamides include the following:

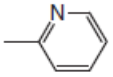
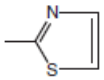
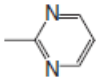
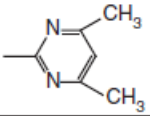
- ✓ Sulphanilamide skeleton is the minimum structural requirement for antibacterial activity.
- ✓ The amino- and sulphonyl-groups on the benzene ring are essential and should be in 4 and 1 position respectively.
- ✓ The N-4 amino group could be modified to be prodrugs, which are converted to free amino function in vivo.
- ✓ Sulphur atom should be directly linked to the benzene ring.

- ✓ Replacement of benzene ring by other ring systems or the introduction of additional substituents on it decreases or abolishes its activity.
- ✓ Exchange of the –SO2NH group by –CONH reduces the activity.
- ✓ On N-1-substituted sulphonamides, activity varies with the nature of the substituent at the amino group.



  - With substituents imparting electron-rich characters to SO2 group, bacteriostatic activity increases.
  - Heterocyclic substituents lead to highly potent derivatives (Sulphapyridine, Sulfathiazole, Sulfadiazine, etc), while sulphonamides, which contain a single benzene ring at N-1 position, are considerably more toxic than heterocyclic ring analogues.

I. N-1 Substituted sulphonamides

Name	R	R^1
Sulphanilamide	–H	–H
Sulphapyridine	–H	
Sulphathiazole	–H	
Sulphacetamide	–H	$-COCH_3$
Sulphadiazine	–H	
Sulphadimidine	–H	

- ✓ The active form of sulphonamide is the ionized, maximum activity that is observed between the pKa values 6.6–7.4.
- ✓ Substitutions in the benzene ring of sulphonamides produced inactive compounds.
- ✓ Substitution of free sulphonic acid (–SO3H) group for sulphonamido function destroys the activity, but replacement by a sulphinic acid group (–SO2H) and acetylation of N-4 position retains back the activity.

15.1.4. Drug Classification of Sulfonamides

Based on Duration of Action

(I) Well absorbed sulphonamides: These are subclassified into

(a) Short acting sulphonamides (half-life less than 20 h): These sulphonamides are rapidly absorbed and rapidly excreted, e.g. Sulphadiazine, Sulphadimidine (sulphamethazine), Sulphamerazine, Sulphisoxazole, Sulphasomidine.

These sulphonamides are used for the treatment of urinary tract infections (since they are excreted in urine in high conc).

(b) Intermediate acting sulphonamides (half-life between 10–24 h): e.g. Sulphamethoxazole and Sulphaphenazole.

(c) Long acting sulphonamides (half-life greater than 24 h): e.g. Sulphadoxine, Sulphadimethoxine and Sulphamethoxydiazine.

(d) Extra long-acting sulphonamides (half-life greater than 50 h): Sulphasalazine, Sulphaclomide, Sulphalene.

(II) Poorly abosorbed sulphonamides: e.g. Succinylsulphathiazole, Phthalylsulphathiazole and Sulphasalazine

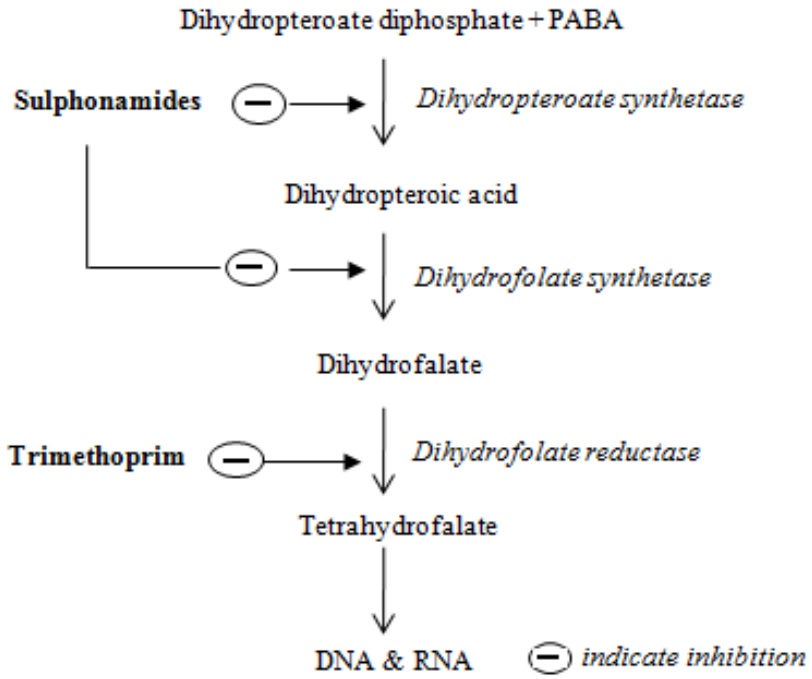
(III) Sulphonamides for topical use: e.g. Silver sulphadiazine and Sulphacetamide

Based on the site of action

- ✓ **Sulphonamides for general infection**: Sulphanilamide, Sulphapyridine, Sulphadiazine, Sulphamethoxacine, Sulphamethoxazole.
- ✓ **Sulphonamides for urinary tract infections**: Sulphaisoxazole, Sulphathiazole.
- ✓ **Sulphonamides for intestinal infections**: Phthalylsulphathiazole, Succinyl sulphathiazole, Sulphasalazine.
- ✓ **Sulphonamides for local infections**: Sulpahacetamide, Mafenamide, Silver sulphadiazine.
- ✓ **Sulphonamides for dermatitis**: Dapsone, Solapsone.
- ✓ **Sulphonamides in combination**: Trimethoprim with Sulphamethoxazole

15.1.5. Mechanism of Action

Sulphonamides contain the sulfanilamide moiety which is a structure analogue of para aminobenzoic acid (PABA), an essential precursor in the synthesis of folic acid in the microorganism. Folic acid is the essential for the synthesis of the DNA and RNA (i.e., growth and multiplication) both in human and in bactaria, but whereas human cannot synthesis, they obtained from diets and taken up by specific uptake mechanism and bacteria as well as asexual form of malarial protozoa, lake of uptake transport system for folic acid they synthesized their own de novo. Therefore, the mammalian cells and microbes which utilize the preformed folic acid are unaffected by sulphonamides.



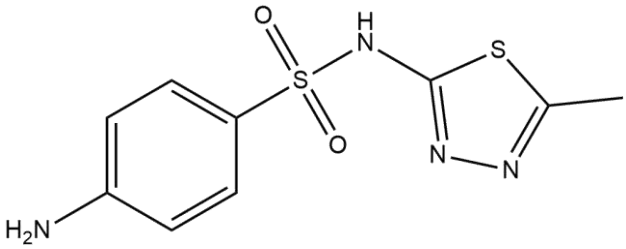
15.1.6. General Uses

Sulphonamides are used in the treatment of urinary tract infections, bacillary dysentry, burns, malaria, conjuctivitis, nocardiasis, Streptococcal infection, gum infection and meningitis.

- ✓ **In inflammatory bowel diseases**: Sulfasalazine, Sulfapyridine with aminosalicylate in combination
- ✓ **In infected burn**: Silver sulfadiazine topically
- ✓ **In urinary tract infection, respiratory tract infection**: Sulphamethoxazole, Sulphisoxazole.
- ✓ Sulphadiazine, Sulfadoxine and Sulfamethopyrazine in combination with Pyrimethamine in treatment of **malaria** (Chloroquine resistant P. falciparum) and **toxoplasmosis**

15.1.7. Medicinal Chemistry of Sulfonamide

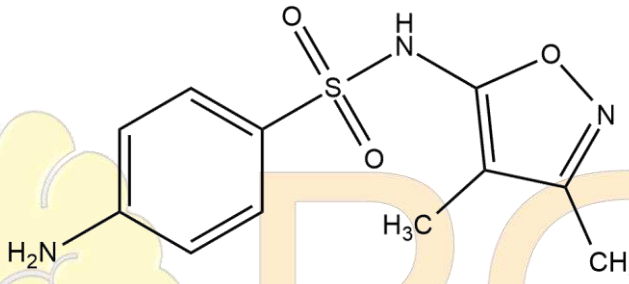
A) Sulphamethizole



4-amino-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide

Uses: UTI

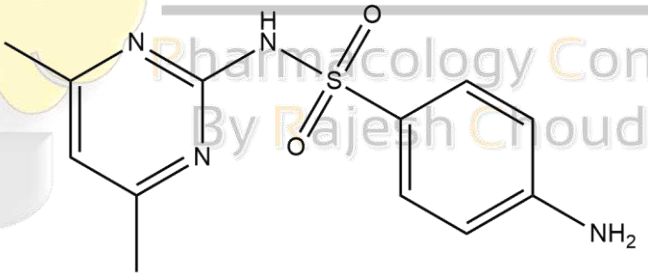
B) Sulfisoxazole



4-amino-*N*-(3,4-dimethyl 1,2-oxazol-5-yl)benzenesulfonamide

Uses: UTI, along with erythromycin used for treatment of **acute otitis media** in children.

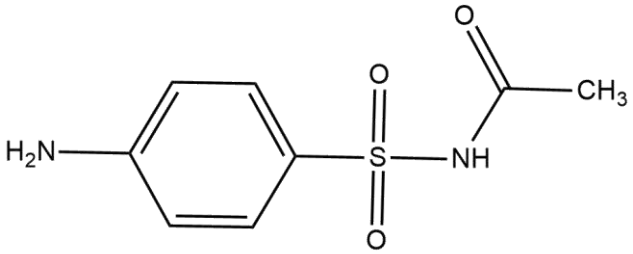
C) Sulphamethizine



4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide

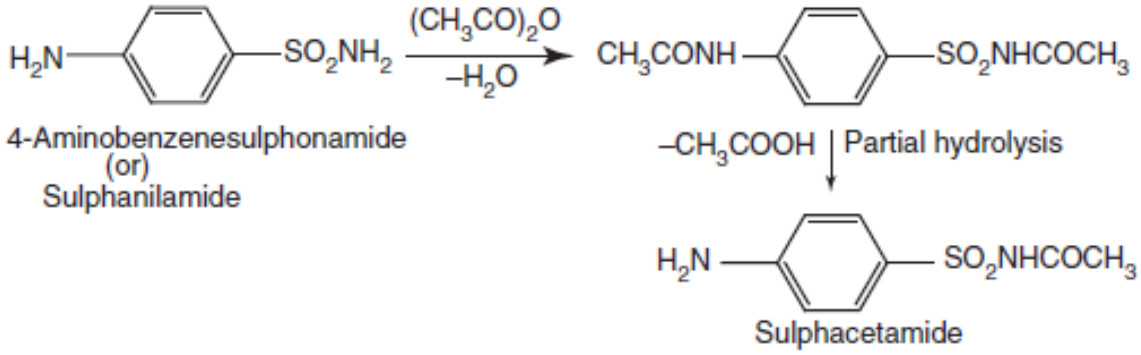
Uses: Bronchitis, prostatitis, and UTI

D) Sulfacetamide*



N-((4-aminophenyl)sulfonyl)acetamide

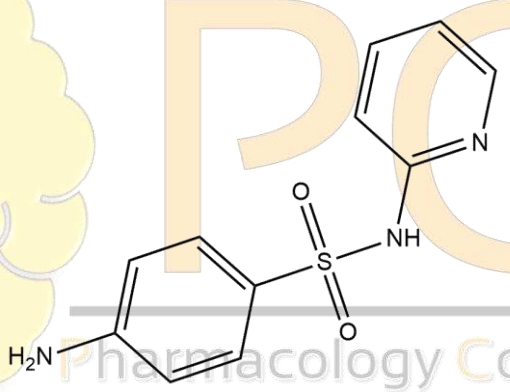
Synthesis



Uses:

- ✓ 10% topical lotion for acne and seborrheic dermatitis
- ✓ Eye drops for conjunctivitis

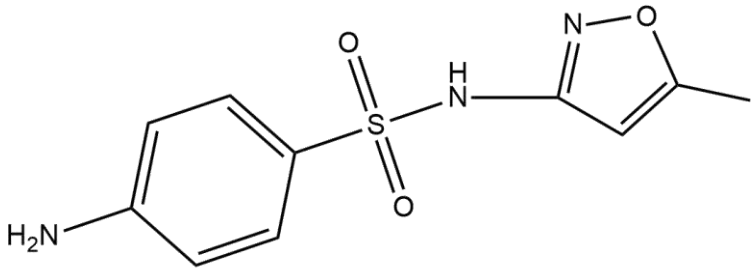
E) Sulphapyridine



4-amino-*N*-(pyridin-2-yl)benzenesulfonamide

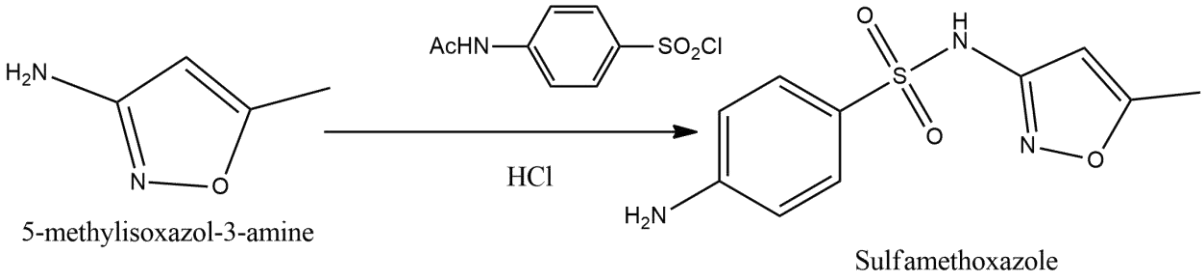
Uses: Certain skin diseases (due to toxicity not used currently)

F) Sulfamethoxaole*



4-amino-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide

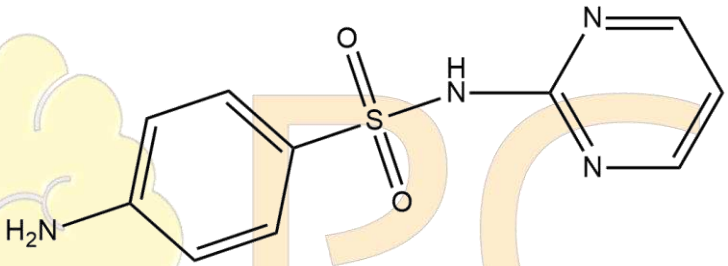
Synthesis



Uses:

- ✓ Bronchitis, prostatitis, and UTI. Used along with Trimethoprim (Cotrimoxazole) for several Gram + and Gram – Bacterial.
- ✓ Along with pyrimethamine used in Malaria

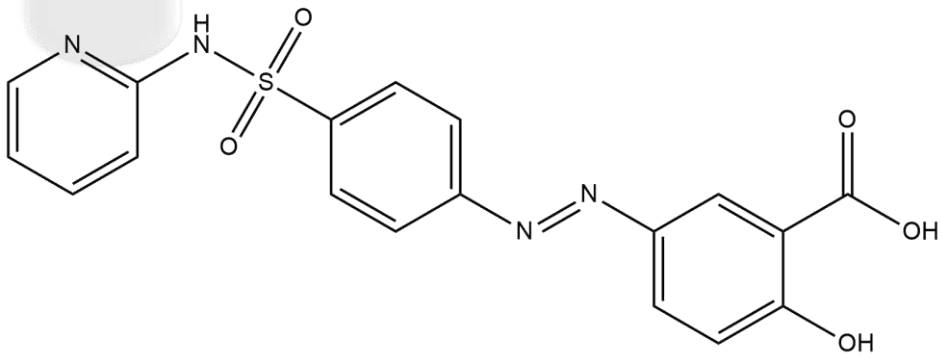
G) Sulphadiazine



4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide

Uses: UTI and Burn. Along with pyrimethamine used in toxoplasmosis caused by Toxoplasma gondii

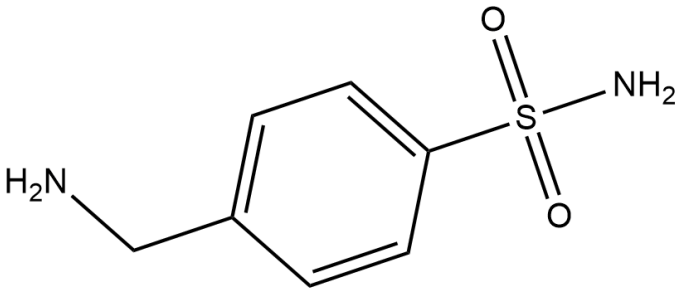
H) Sulfasalazine



(*E*)-2-hydroxy-5-((4-(*N*-(pyridin-2-yl)sulfamoyl)phenyl)diazenyl)benzoic acid

Uses: Inflammatory Bowel Diseases (Ulcerative colitis and Crohn's Disease). It is also used in rheumatoid arthritis.

I) Mefenide

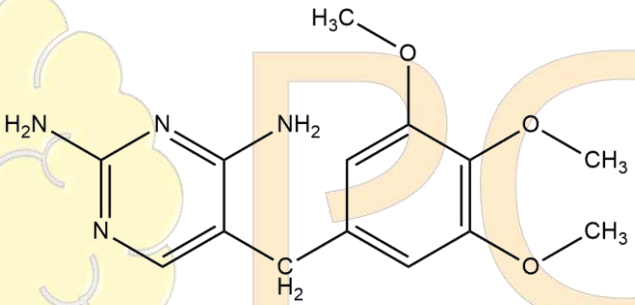


4-(aminomethyl)benzenesulfonamide

Uses: In severe burns and other gram + and gram – bacterial infection.

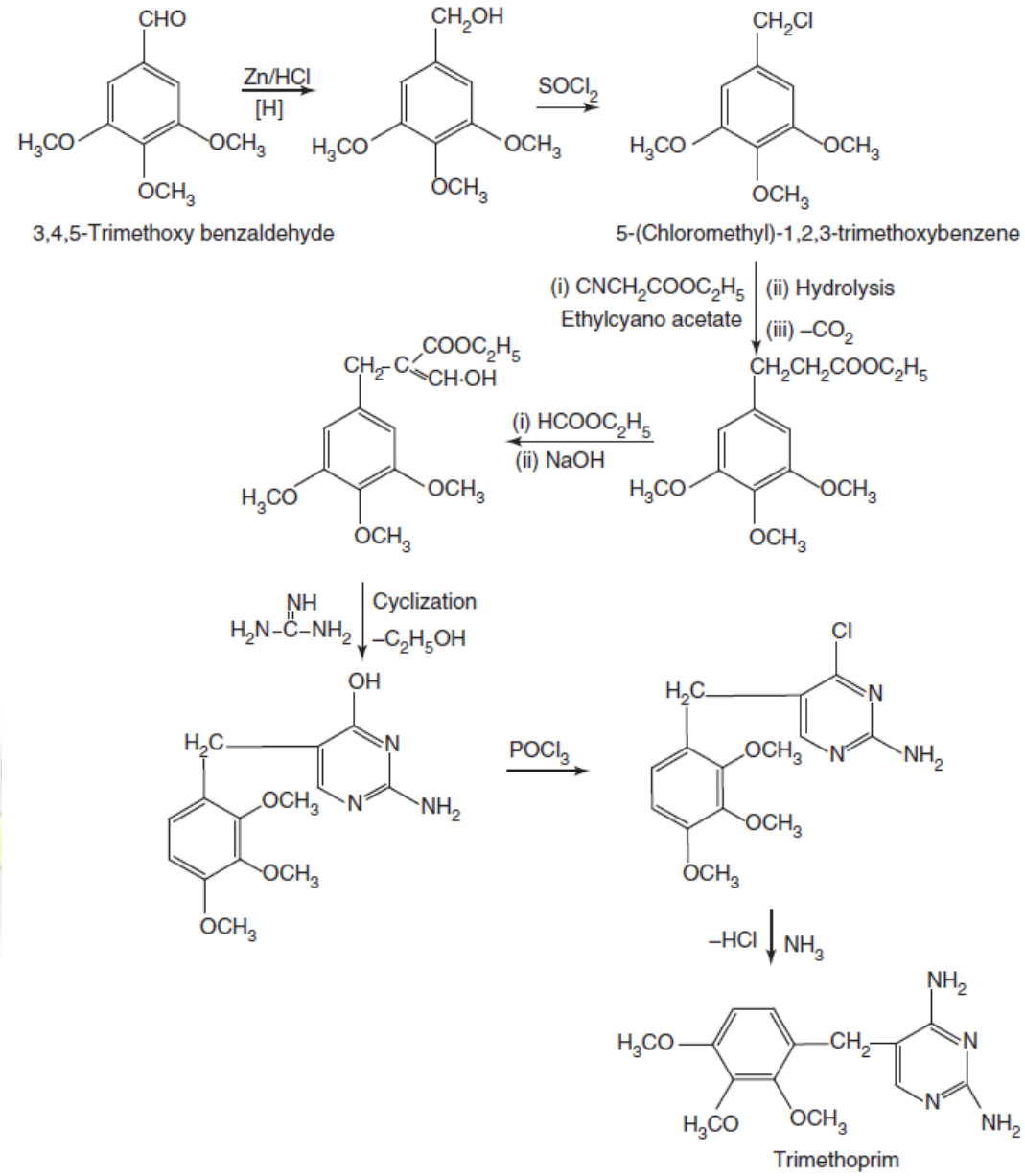
15.2. FOLATE REDUCTASE INHIBITORS & SULFONES

A) Trimethoprim*



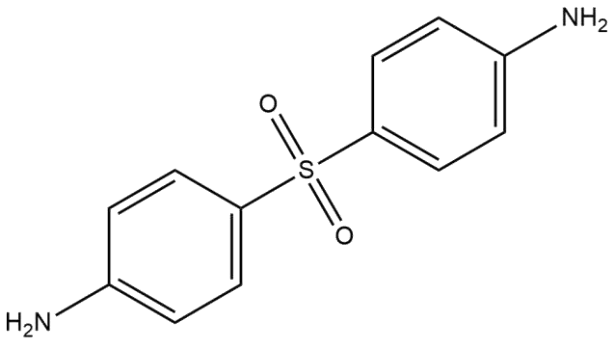
5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine

- Trimethoprim is a **diaminopyrimidine** which is related to antimalarial drug like **pyrimethamine**, they are selective inhibitor of **bacterial dihydrofolate reductase (DHFR)** and further inhibit the thymidylate synthesis.
- Trimethoprim is absorbed from gut and distributed widely in body fluids and tissues. It is more concentrated in prostatic and vaginal fluids, which are more acidic in nature than plasma. Therefore, it has more antibacterial activity in **prostatic and vaginal fluids** than other AMAs.



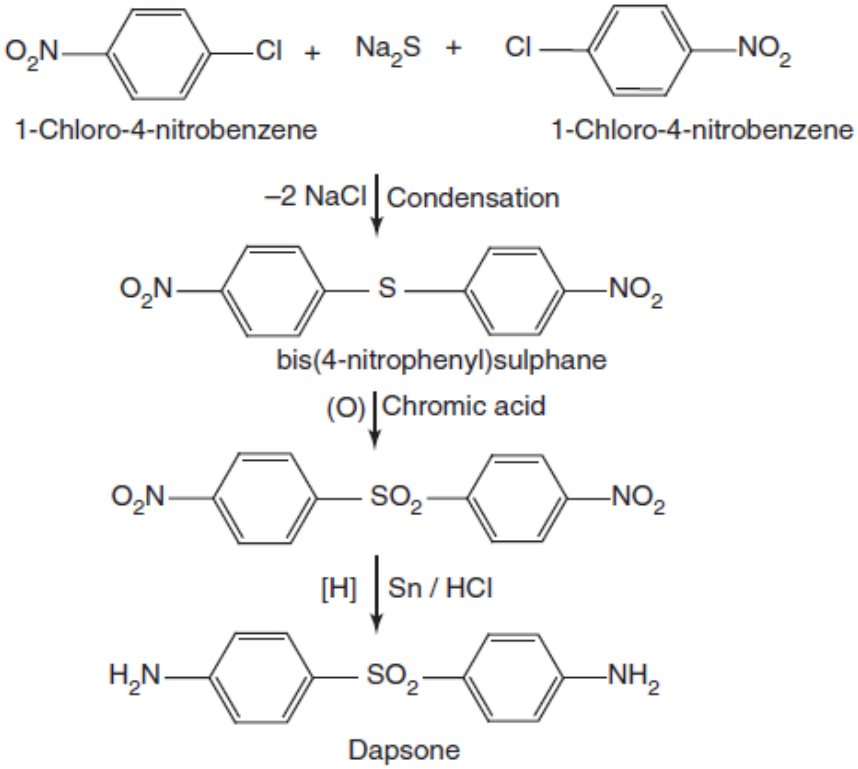
B) Cotrimoxazole: Co-trimoxazole contains sulphamethoxazole and trimethoprim in 5:1 proportion. Sulfamethoxazole with trimethoprim produces sequential blocking of DHFS and DHFR in folic acid synthesis, resulting in marked enhancement of the activity of both drugs. It is indicated for treating infection of the urinary, gastrointestinal & respiratory tracts. Combination of the two, i.e; sulphamethoxazole and trimethoprim produce bactericidal/bacteriostatic action.

C) Sulfones: Dapsone



4,4'-sulfonyldianiline

Synthesis



- It inhibit the folic acid synthesis by inhibiting the DHFS enzyme similar as sulfonamide.
- Dapsone is a sulfone with anti-inflammatory immunosuppressive properties as well as antibacterial and antibiotic properties.
- Dapsone is the principal drug in a multidrug regimen recommended by the World Health Organization for the treatment of leprosy.
- As an anti-infective agent, it is also used for treating malaria and, recently, for Pneumocystic carinii pneumonia in AIDS patients

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