

# **Sulphonamide, Sulphone & Folate reductase Inhibitors**

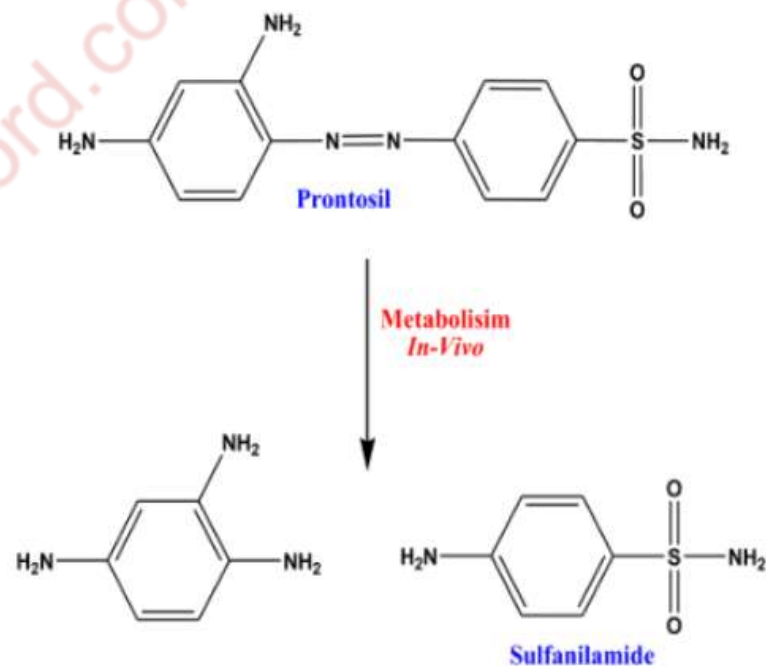
**Presented By:-**

**Mr. Samarpan Mishra (Assistant Professor)**

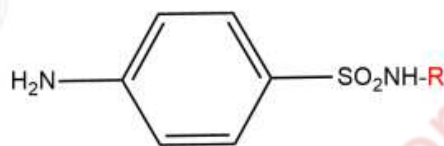
**Specialization - Pharmaceutical Chemistry**

## 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.
- ❑ Prontosil → 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 antibacterial active agent.



## SAR of Sulphanilamide

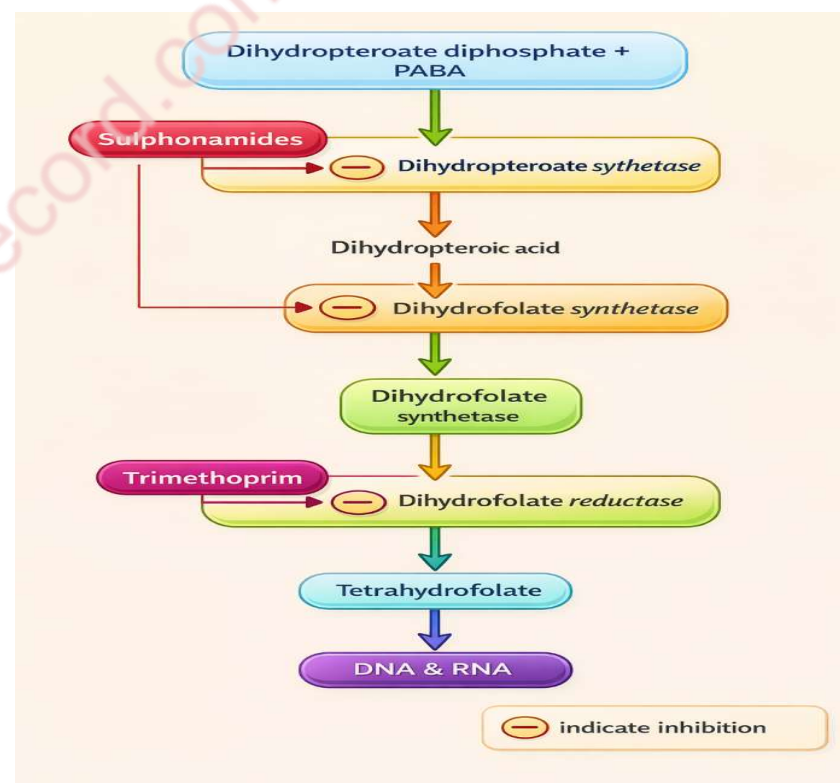


1. Sulphanilamide skeleton is the minimum structural requirement for antibacterial activity.
2. The **amino-** and **sulphonyl groups** on the benzene ring are essential and should be in 4 and 1 position respectively.
3. The **N-4 amino group** could be modified to be prodrugs, which are converted to free amino function *in vivo*.
4. **Sulphur atom** should be directly linked to the benzene ring.
5. **Replacement of benzene ring** by other ring systems or the introduction of additional substituents on it decreases or abolishes its activity.
6. Exchange of the **-SO<sub>2</sub>NH group** by **-CONH** reduces the activity.
7. On **N-1-substituted sulphonamides**, activity varies with the nature of the substituent at the amino group.

## MOA of Sulphanilamide

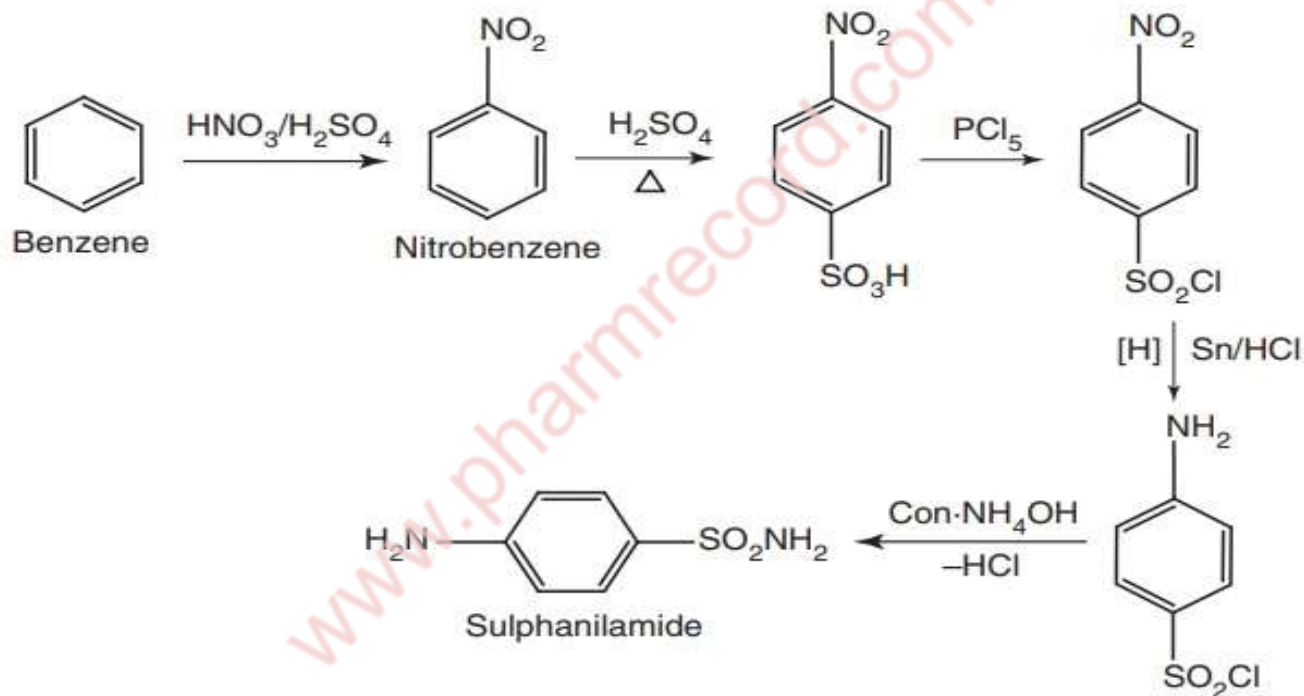
Sulphonamides contain the sulfanilamide moiety which is a structural analogue of para aminobenzoic acid (PABA), an essential precursor in the synthesis of folic acid in the microorganism. Folic acid is essential for the synthesis of DNA and RNA (i.e., growth and multiplication) both in humans and in bacteria, but whereas humans cannot synthesize it, they obtain it from diet and take it up by specific uptake mechanisms. Bacteria, as well as asexual forms of malarial protozoa, lack a transport system for folic acid and therefore synthesize their own *de novo*.

Therefore, the mammalian cells and microbes which utilize preformed folic acid are unaffected by sulphonamides.

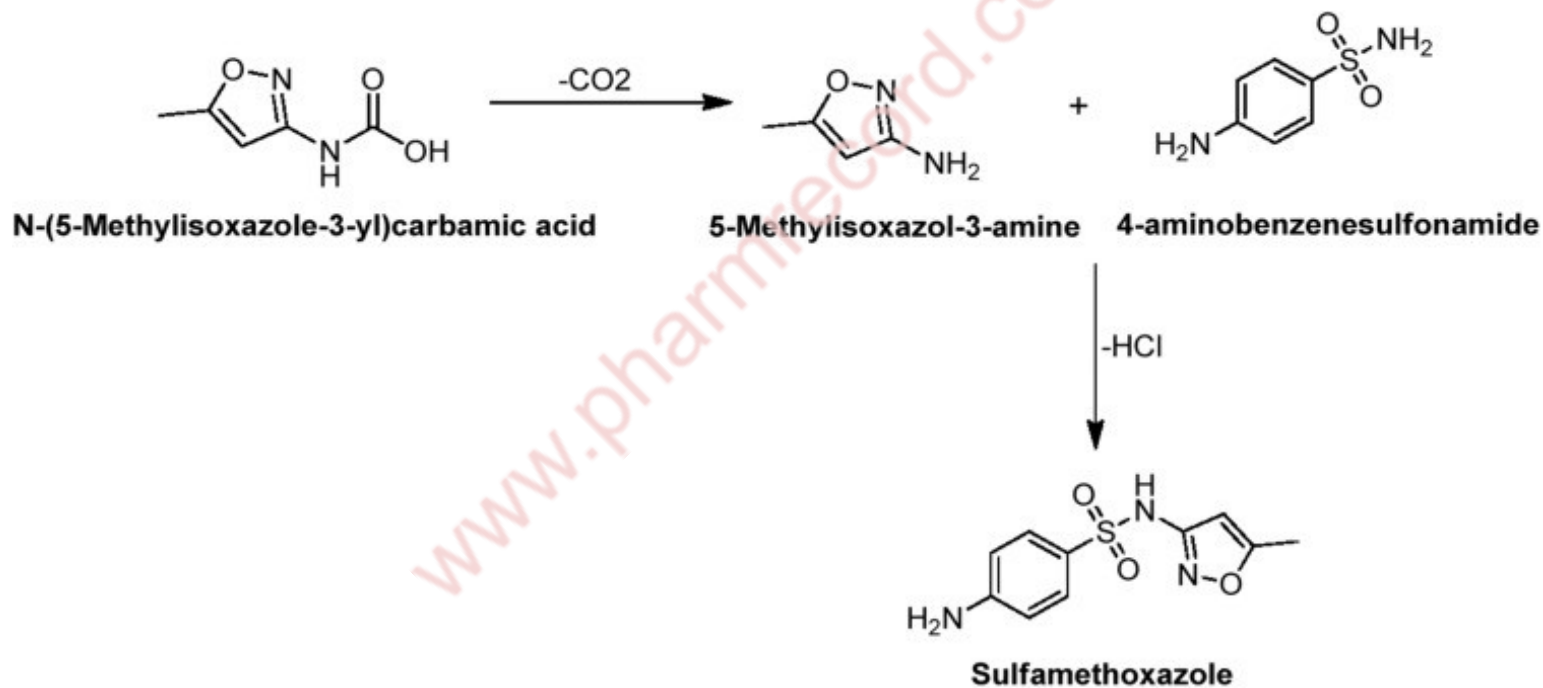


Drug	Mechanism of Action (MOA)	Clinical Uses
Sulphamethizole	Inhibits bacterial dihydropteroate synthase → blocks folic acid synthesis	Primarily used in urinary tract infections (UTIs)
Sulfisoxazole	Inhibits dihydropteroate synthase, bacteriostatic	Used for UTIs, otitis media (often with erythromycin in children)
Sulphamethazine	Inhibits folic acid synthesis by targeting dihydropteroate synthase	Veterinary use mostly; occasionally for systemic infections
Sulfacetamide*	Inhibits bacterial folate synthesis	Topical use for eye infections (conjunctivitis, trachoma), acne
Sulphapyridine	Inhibits folic acid synthesis	Component of sulfasalazine; used in rheumatoid arthritis and inflammatory bowel diseases
Sulfamethoxazole*	Inhibits dihydropteroate synthase; used in combination with trimethoprim (TMP-SMX)	UTIs, respiratory infections, Pneumocystis pneumonia (PCP), toxoplasmosis
Sulphadiazine	Inhibits folic acid synthesis	Used with pyrimethamine for toxoplasmosis; also used for burn wound prophylaxis
Mefenide acetate	Inhibits bacterial carbonic anhydrase and folic acid synthesis	Topical use for burns to prevent infection
Sulfasalazine	Broken into sulfapyridine and 5-aminosalicylic acid in colon	Ulcerative colitis, Crohn's disease, rheumatoid arthritis

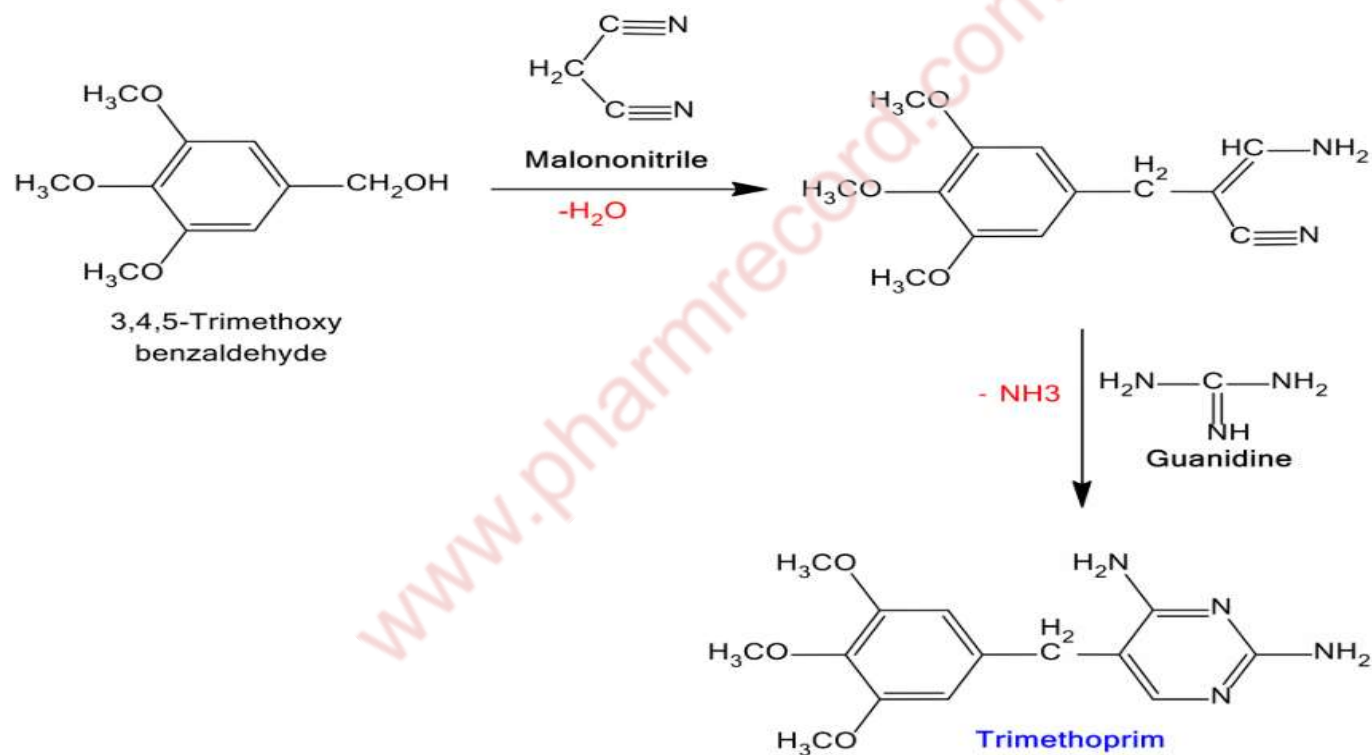
# Synthesis of Sulfacetamide



## Synthesis of Sulfamethoxazole



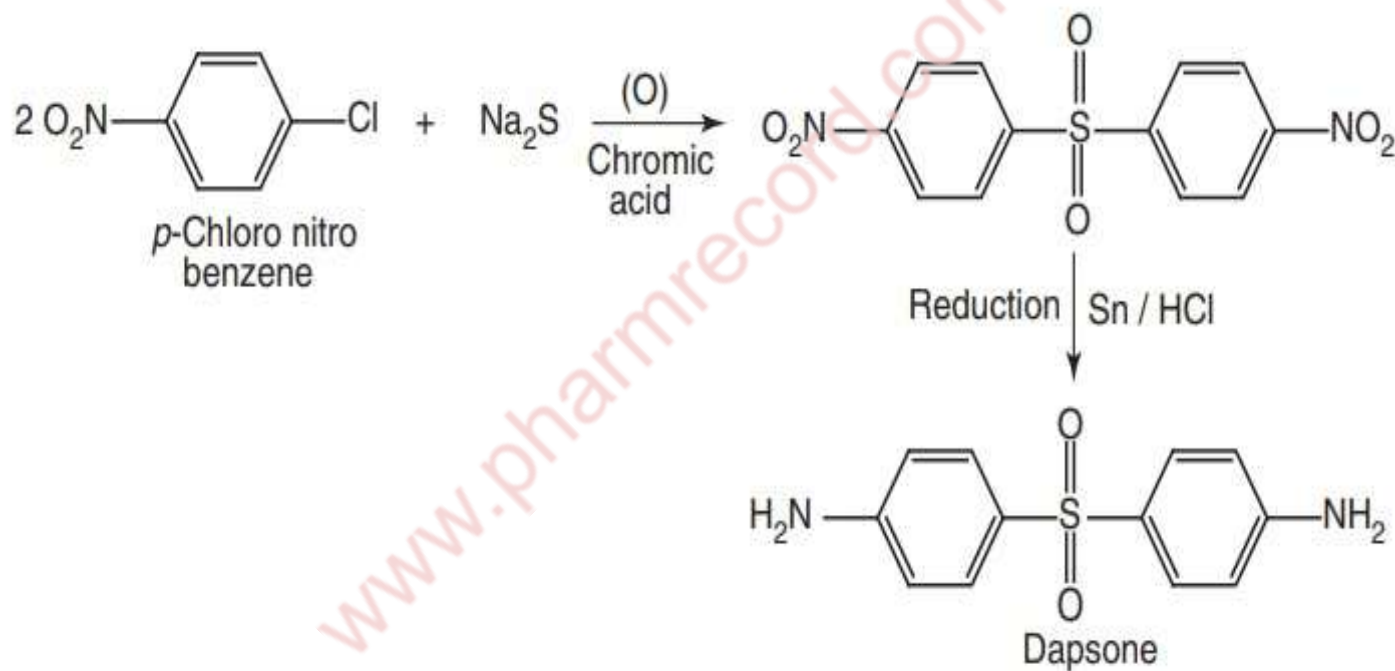
## Synthesis of Trimethoprim



# Dapsone

<b>Introduction</b>	<b>Mechanism of Action (MOA) of Dapsone</b>
<ol style="list-style-type: none"><li>1. <b>Dapsone</b> is a <b>synthetic sulfone drug</b> with antibacterial and anti-inflammatory properties.</li><li>2. Chemically related to <b>sulphonamides</b> (PABA analog).</li><li>3. It is <b>bacteriostatic</b> in action.</li><li>4. Mainly used in:<ul style="list-style-type: none"><li>• <b>Leprosy</b> (<i>Mycobacterium leprae</i>)</li><li>• <b>Dermatitis herpetiformis</b></li><li>• <b>Pneumocystis jirovecii pneumonia (PCP)</b> (alternative therapy)</li></ul></li></ol>	<ol style="list-style-type: none"><li>1. Dapsone acts as a <b>competitive antagonist of PABA (para-aminobenzoic acid)</b>.</li><li>2. It <b>inhibits the enzyme dihydropteroate synthase</b> in bacteria.</li><li>3. This blocks the synthesis of: <b>Dihydropteroic acid → Dihydrofolic acid → Tetrahydrofolate</b></li><li>4. <b>Effect of inhibition:</b><ul style="list-style-type: none"><li>• ↓ Folic acid synthesis</li><li>• ↓ DNA &amp; RNA synthesis</li><li>• ↓ Bacterial growth (bacteriostatic effect)</li></ul></li></ol>

## Synthesis of Dapsone



**THANK YOU**

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