Anthelmintics

Helminthiasis is an infection caused by helminths to human body.

Helminth is a general term for worms.

Anthelmintics are drugs used against the parasitic worms. Those drugs which kill the parasites are called vermicides and those which remove or expel the parasites from the body are vermifuses.

→ Helminths mostly attack GI tract.

→ The worm parasites of humans belong to two phyla, nematodes and platyhelminthes.

Classification of Anthelmintic Drugs

1) Piperazines :- Diethylcarbamazine citrate (DEC), Piperazine citrate.
2) Benzimidazoles :- Albendazole, Mebendazole, Thiabendazole.
3) Heterocyclics :- Oxamniquine, Praziquantel.
4) Natural Products :- Ivermectin and Avermectin.
5) Amide :- Niclosamide
6) Vinyl Pyrimidines :- Pyrantel and oxantel.

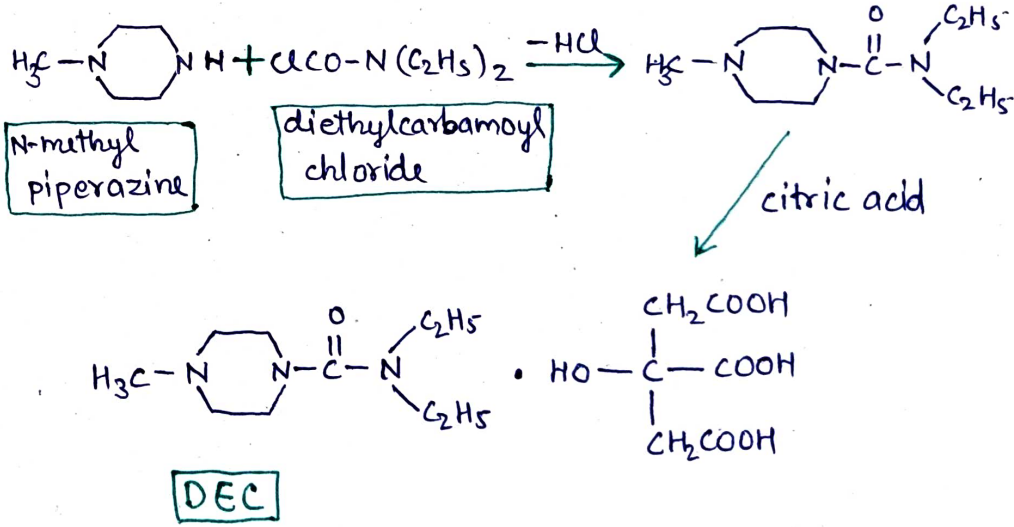
Major Drugs

1) Diethylcarbamazine citrate
2) Thiabendazole
3) Mebendazole
4) Albendazole
5) Niclosamide
6) Oxamniquine
7) Praziquantel
8) Ivermectin

Diethylcarbamazine Citrate *

DEC is used for treating filariasis, specially in invasions of Wuchereria bancrofti or Loa loa.

synthesis



MoA

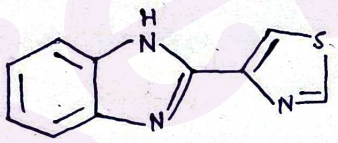
DEC prevents neural transmission in the worm causing muscular paralysis and expelling the worms alive.

Uses

→ ascariasis, filariasis, lymphatic filariasis

side effects include fever swollen glands in neck, skin rash, nausea and dizziness.

Thiabendazole



It is a broad-spectrum anthelmintic agent used in the treatment of intestinal pinworm and strongyloidiasis.

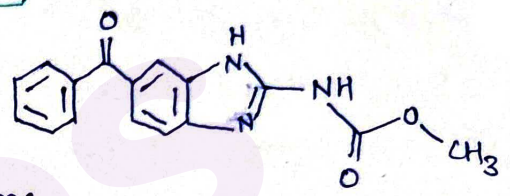
MoA

Thiabendazole has been shown to inhibit the helminth-specific enzyme, fumarate reductase.

Uses

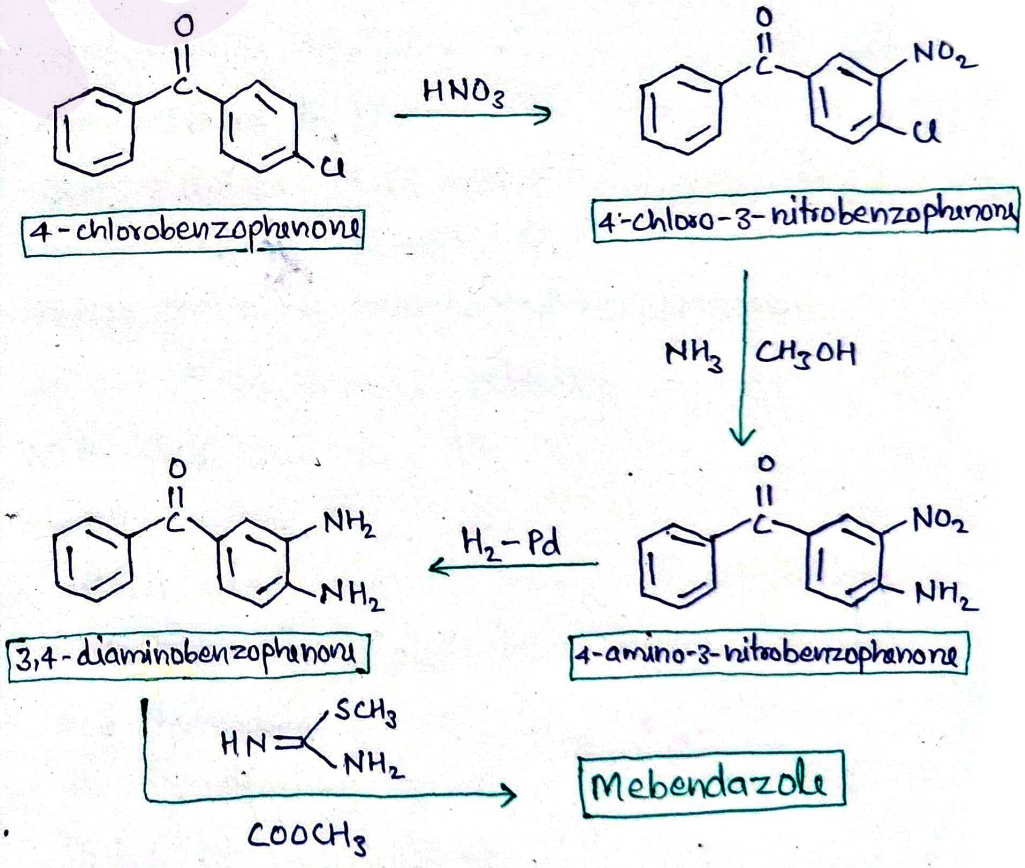
Treatment of strongyloides infection, cutaneous larva migrans, visceral larva migrans and trichinosis.

Mebendazole *



It is used mainly for the infections of gut such as threadworms (pinworms) and other less common worm infections (whipworm, roundworm, hookworm).

synthesis



MOA

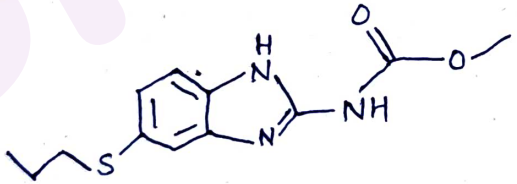
Mebendazole interferes with the metabolism of carbohydrates and inhibits the polymerisation of of cytoplasmic microtubules, which are required for promoting glucose uptake in the parasites. As a result, glycogen stores of the parasite is depleted which hinders its survival.

Uses

Mebendazole is used in treating ascariasis, pinworm infection, hookworm infections, guinea worm infections, hydatid disease and giardia.

Albendazole

It is an anthelmintic medication which treat various worm infections.



MOA

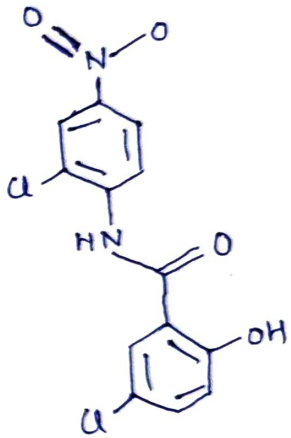
It is similar to mebendazole.

It works by preventing the worm from absorbing sugar (glucose), so that worm loses energy and dies.

Uses

→ It is used for cystic hydatid disease of liver, lung and peritoneum, caused by the larval form of Echinococcus granulosus (dog tapeworm).

Niclosamide



It is used for most tapeworm infections.

MOA

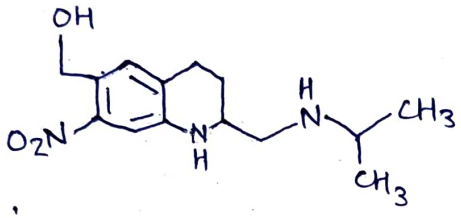
Niclosamide has been demonstrated to block glucose uptake, thus acting as an uncoupling agent for energy-generating oxidative phosphorylation in intestinal worms, starving the worms of ATP. And then they die.

Uses

→ It is used to treat tapeworm infestations, including diphyllobothriasis, hymenolepiasis and taeniasis.

→ Its not effective against other worms such as flukes or roundworms.

Oxamniquine



It is a medication used to treat schistosomiasis caused due to Schistosoma mansoni.

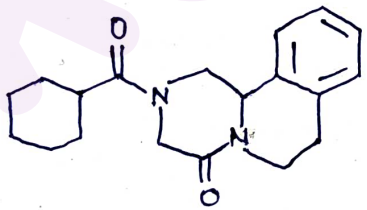
MoA

Oxamniquine causes an irreversible inhibition of nucleic acid metabolism of the parasites.

Uses → schistosomiasis

common side effects.

Praziquantel



It is used in most schistosome and many cestode infestations.

MoA

It works by causing severe spasms and paralysis of worm's muscles due to rapid Ca^{2+} influx inside the schistosome.

Uses

Praziquantel is used for the treatment of infections due to all species of schistosoma.

common side effects like headache, dizziness, stomach upset, nausea, tiredness.

Ivermectin

It is a broad-spectrum anti-parasite, used to treat certain parasitic roundworm infections.

MoA

Ivermectin induces paralysis of the musculature of the parasites by binding to the chloride ion channels of the muscle cells.

Uses

→ used in the treatment of onchocerciasis.

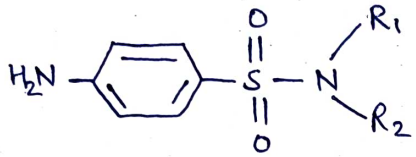
→ suitable for the treatment of intestinal strongyloidiasis caused by strongyloides stercoralis.

→ used to treat scabies caused by sarcoptes scabiei.

common side effects.

Sulphonamides

Sulphonamides are also called sulpha drugs. These are synthetic antimicrobial agents containing sulphonamide group.



Sulphonamide group

→ Sulphonamides are used for preventing and treating bacterial infections.

→ Structurally, sulphonamide resembles p-Amino-benzoic Acid (PABA).

History

→ Prontosil was the first sulphonamide.

→ Sulphonamide drugs were first discovered by German chemist Gerhard Domagk in 1930s.

→ They were widely used in World War II to treat wounded soldiers and civilians, significantly reducing mortality rates.

→ Over time bacteria developed resistance to sulphonamides, limiting their effectiveness. This led to the development of newer antibiotics.

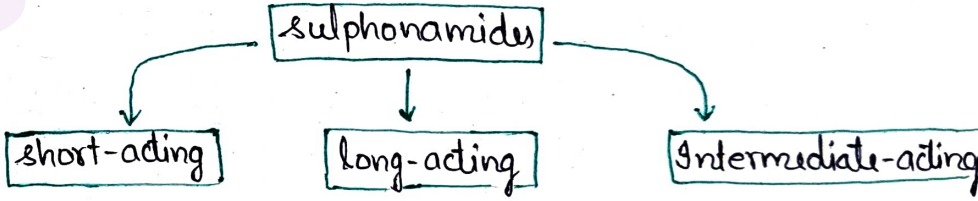
Chemistry of sulphonamides

Chemically sulpha drugs are amphoteric. They behave as weak organic acid with pKa ranging from 4.79 to 8.56. They are weakly soluble in water but their solubility increases at alkaline pH.

→ Their sodium salts are easily soluble in water.

Classification

Based on their duration of action.

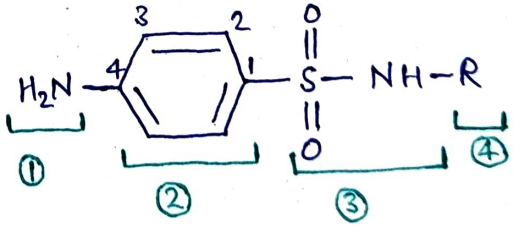


4-8 hours
e.g. Sulphadiazine
Sulphamethoxazole

8-16 hours
e.g.
Sulphaphenazole

1-7 days of duration of action.
e.g.
Sulphadimethoxine

SAR of Sulphonamides



① p-Amino group
② Aromatic ring
③ Sulphanilamide group
④ N'-substitution group

→ The amino and sulphonyl group (O=S=O) on the benzene ring are essential and should be at 4th and 1st position respectively.

→ Replacement of aromatic ring by other ring systems or the introduction of additional substituents on it decreases activity.

→ Exchange of the $-SO_2NH$ group by $-CONH$ reduce the activity.

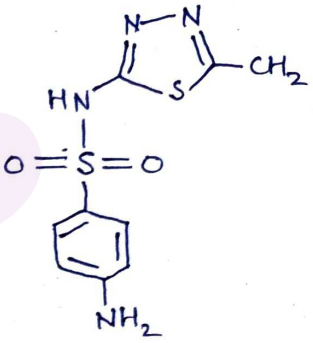
→ Substitution of aromatic heterocydic nuclei at N' yields highly potent compounds.

→ N'-di substitution leads to complete inactivity.

Major Drugs

1) Sulphamethizole
2) Sulfisoxazole
3) Sulphamethazine
4) Sulphacetamide
5) Sulphapyridine
6) Sulphamethoxazole
7) Sulphadiazine
8) Mafedine acetate
9) Sulphasalazine

Sulphamethizole



It is an antibacterial sulfonamide.

MOA

Sulphamethizole is a competitive inhibitor of bacterial enzyme, dihydropteroate synthetase enzyme. The normal PABA binding is prevented. This inhibited reaction reaction in these organisms is necessary for the synthesis of folic acid. Inhibition of folic acid synthesis stops the bacterial growth.

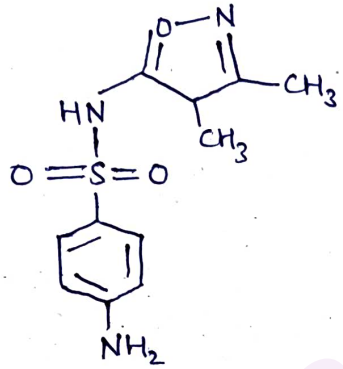
Uses

→ It is a broad-spectrum antibacterial sulfonamide used in the treatment of urinary tract infections.

Side Effects

It includes nausea, vomitting, diarrhoea, vaginitis, dermatitis, allergic reactions, skin rash, red or purple spots under the skin, blood in urine, and swelling of tongue, mouth or rectum.

Sulfisoxazole



It is a broad-spectrum sulfonamide used with other antibiotics in a variety of bacterial infections.

MOA

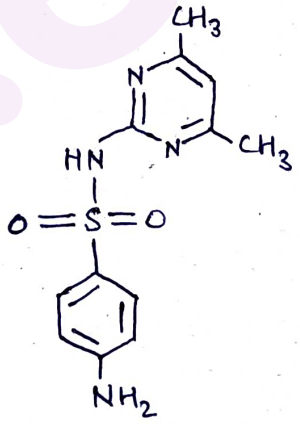
similar to sulphamethizole.

Uses

chancroid, otitis media and urinary tract infections.

common side effects.

sulphamethazine



It is a sulfonamide antibacterial.

MOA

→ Sulphamethazine inhibits the conversion of pteridine and PABA to dihydrofolate synthetase which is an intermediate of tetrahydrofolic acid (THF) synthesis.

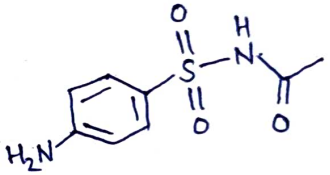
→ THF is required for the synthesis of purines and dTMP and thus, inhibition of its synthesis retards bacterial growth.

Uses

bronchitis, prostatitis and urinary tract infections.

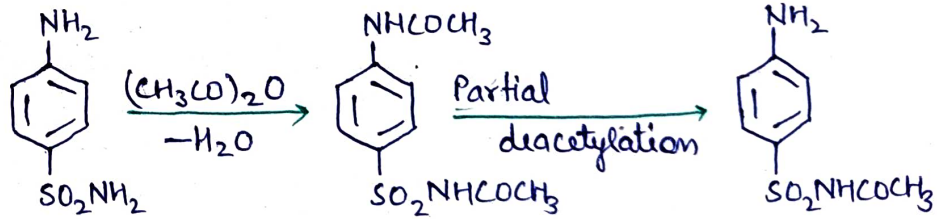
Common side effects.

sulphacetamide *



It is a sulphonamide antibiotic that is used as a cream to treat skin infections and as eye drops to treat eye infections.

synthesis



sulphanilamide → Acetylated sulphanilamide → sulphacetamide

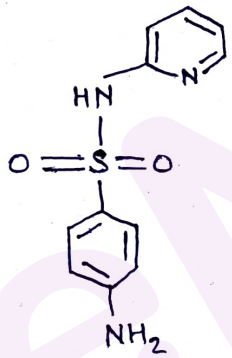
MOA

similar to sulphamethizole.

Uses

used for treating bacterial vaginitis, keratitis, acute conjunctivitis and blepharitis.

sulphapyridine



It is an antibacterial and potentially toxic agent. However, it is no longer prescribed.

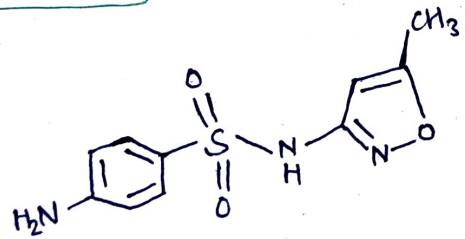
MOA

similar to sulphamethizole.

Uses

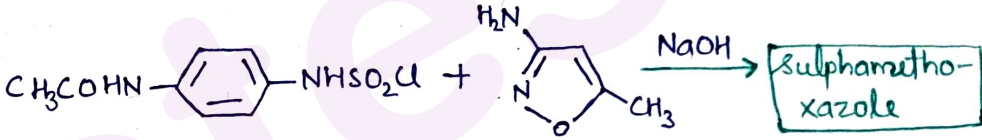
Used in the treatment of dermatitis herpetiformis and pyoderma gangrenosum.

sulphamethoxazole *



It is an oral sulfonamide antibiotic, given in combination with trimethoprim used to treat a variety of infections of the urinary tract, respiratory tract and GI tract.

synthesis



MOA

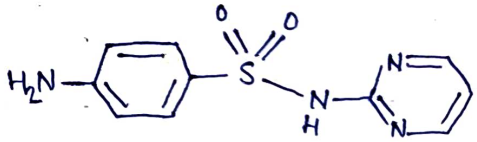
similar to sulphamethazine.

Uses

treat infections causing bronchitis, prostatitis and UTIs.

Common side effects.

sulphadiazine



It is a short-acting bacteriostatic sulphonamide.

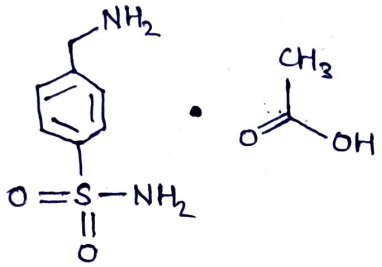
MOA → similar to sulfamethizole.

Uses :- 1) used in the treatment of upper RT infections, otitis media.

2) Treat infections by Haemolytic streptococcus.

Mafenide Acetate

Mafenide is antibacterial agent that is used to treat severe burns.



MOA

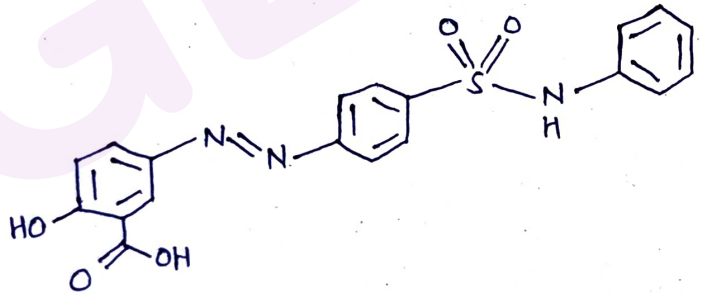
The exact mechanism is not known. However, it is assumed to reduce the bacterial population in the burn tissue and promote healing of deep burns.

Uses

control bacterial infection on burn wounds.

Sulfasalazine

It is used in the management of inflammatory bowel diseases.



Uses

Treatment of Crohn's disease and rheumatoid arthritis as a second-line agent.

MOA

The MOA is not clear, but it appers that sulfasalazine have immunosuppressive, antibacterial and anti-inflammatory effects.

Folate Reductase Inhibitors

Folate Reductase Inhibitors are a class of medications that block the action of enzyme dihydrofolate reductase which is essential for the synthesis of DNA, RNA and proteins.

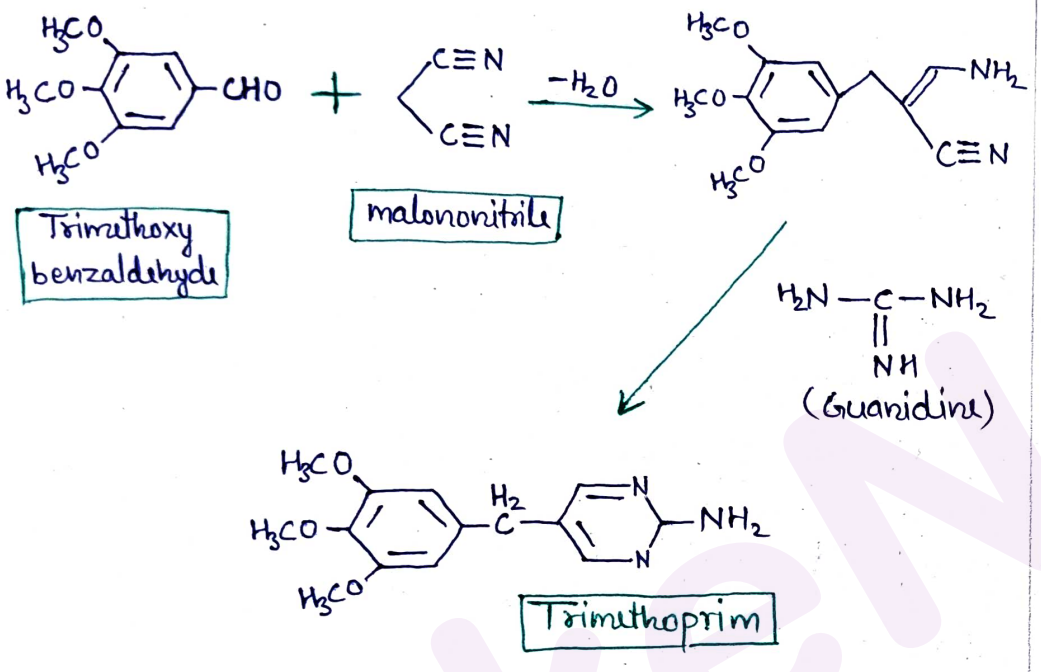
→ They are commonly used as antibiotics to treat bacterial infections and as antineoplastic agents to treat certain types of cancer.

Major drugs

Trimethoprim *

Trimethoprim is an antibiotic commonly used to treat various bacterial infections, particularly those of the urinary tract. It is often given in combination with sulfamethoxazole.

Synthesis



Trimethoxy benzaldehyde

malononitrile

Trimethoprim

MOA

Trimethoprim inhibits dihydrofolate reductase enzyme and prevents the conversion of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF) in thymidine synthesis pathway, which further affects the amino acid metabolism and DNA replication in bacteria.

Uses

1) treatment of UTIs, pylonephritis (with sulfamethoxazole).
2) Treat bacteriuria during pregnancy.

Common side effects.

Cotrimoxazole

Cotrimoxazole is a combination antibiotic often used to treat bacterial infections.

It consists of two antibiotics:

sulfamethoxazole + Trimethoprim → Cotrimoxazole

They work together to target different aspects of bacterial growth.

MOA

Cotrimoxazole works by inhibiting two enzymes essential for bacterial growth:- dihydropteroate synthase (targeted by sulfamethoxazole) and dihydrofolate reductase (targeted by trimethoprim). By blocking these enzymes, cotrimoxazole disrupts the folic acid synthesis, a crucial component for bacterial DNA and protein production, ultimately affecting bacterial replication.

Uses

Cotrimoxazole used to treat UTIs, RTIs, skin and soft tissue infections, traveler's diarrhea, infections caused by the bacteria Pneumocysti jirovecii.

Sulfones

Sulfones are a class of organic compounds containing a sulphonyl functional group (SO_2). An example of sulfone drug is dapsone.

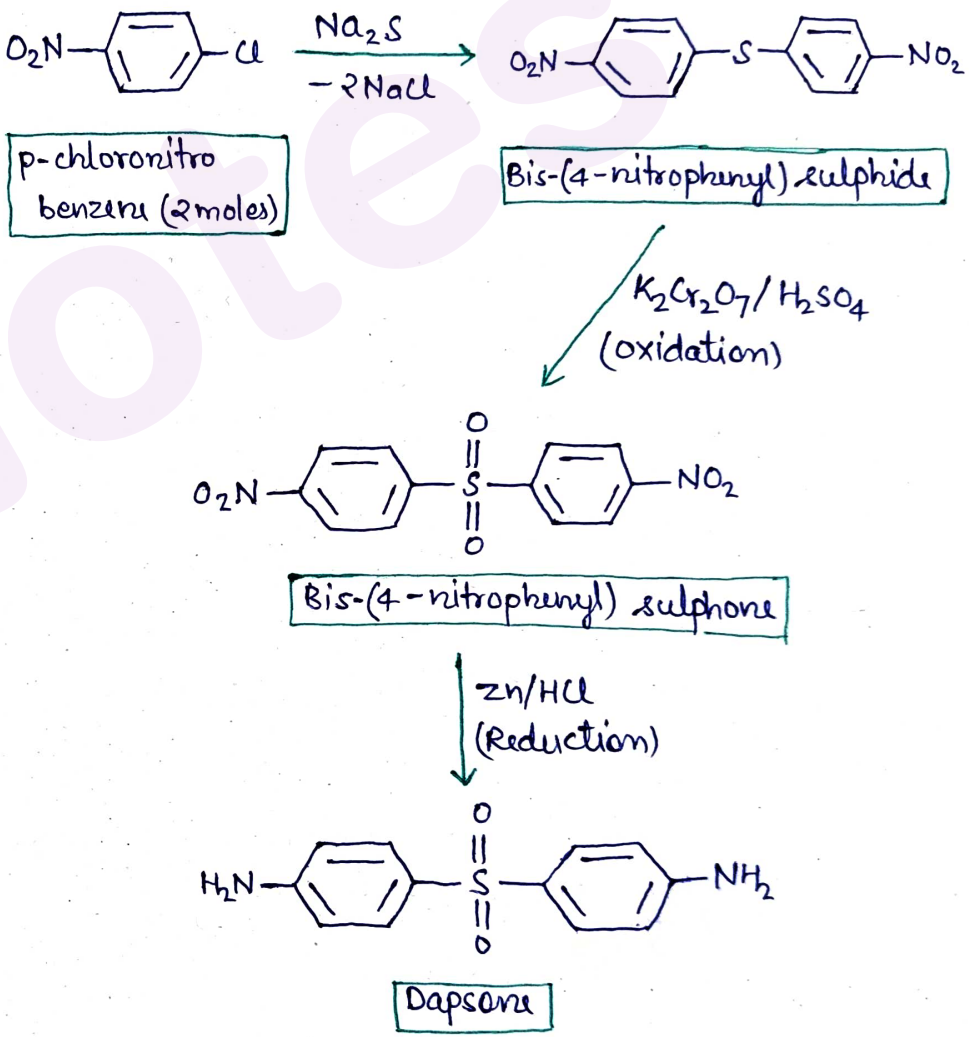
Dapsone

Dapsone is a nearly water-insoluble agent that is very weakly basic. Dapsone is generally well-tolerated but can have side effects like anemia or allergic reactions in some individuals.

MoA

Dapsone inhibits bacterial folate synthesis which disrupts growth and reproduction in bacteria. Additionally, it has anti-inflammatory properties.

Synthesis



Uses

1) Treat leprosy (Hansen's disease) and dermatitis herpetiformis.
2) Also prevent malaria and certain inflammations.