Program	B. Pharmacy
Semester	VI
Subject /Course	Medicinal Chemistry III
Subject/Course ID	BP 601T
Module No.	04
Module Title	Antifungal antibiotics
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Learning Outcome of module-4

LO	Learning Outcome (LO)	Course Outcome Code
LO1	To Understand the Nomenclature &chemistry of drugs with respect to their biological activity.	BP601.1
LO2	To understand the importance of SAR of drugs.	BP601.4
LO3	To understand the Basic concepts and application of prodrugs design.	BP601.3

Content

Topics
Antifungal Antibiotics Amphotericin-B, Nystatin, Natamycin, Griseofulvin. Synthetic Antifungal Agents Clotrimazole, Econazole, Butoconazole, Oxiconazole Tioconozole, Miconazole*, Ketoconazole, Terconazole, Itraconazole, Fluconazole, Naftifine hydrochloride, Tolnaftate*.
Anti-Protozoal Agents Metronidazole*, Tinidazole, Ornidazole, Diloxanide, Iodoquinol, Pentamidine Isethionate, Atovaquone, Eflornithine.
Anthelmintics Diethylcarbamazine citrate*, Thiabendazole, Mebendazole*, Albendazole, Niclosamide, Oxamniquine, Praziquantal, Ivermectin.
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*.

ANTIFUNGAL ANTIBIOTICS

An **antifungal** medication, also known as an antimycotic medication, is a pharmaceutical fungicide or fungistatic used to treat and prevent mycosis such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others.

Classification of Antifungal Drugs

1- Antifungal Antibiotics :

- Griseofulvin
- Polyene macrolide : Amphotericin- B & Nystatin

2- Synthetic :

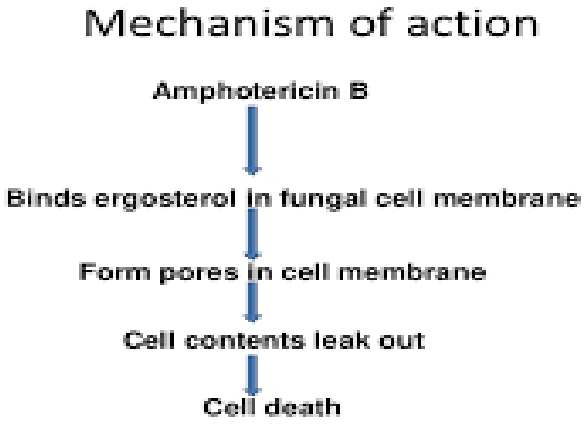
- Azoles :

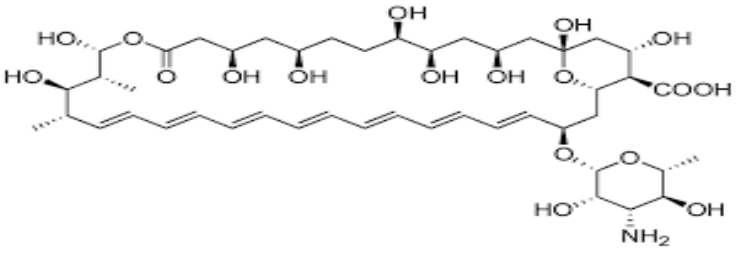
A) Imidazoles : Ketoconazole , Miconazole

B) Triazoles : Fluconazole , Itraconazole

Drugs

1. **Amphotericin-B**





Amphotericin B

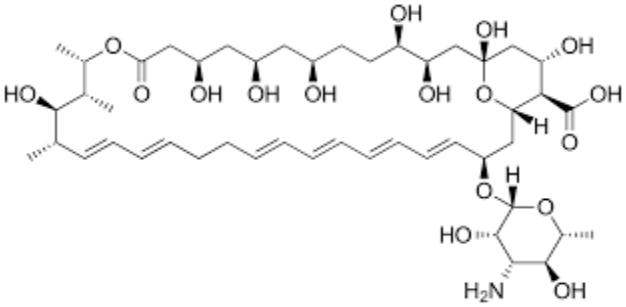
USES

- Amphotericin B can be applied topically for oral, vaginal and cutaneous candisasis and otomycosis.
- It is the most effective drug for various types of systemic mycosis and is the gold standard of antifungal therapy. However, because of higher toxicity of amphotericin B, the azole antifungals are now preferred in conditions where their efficacy approaches.

2. Nystatin

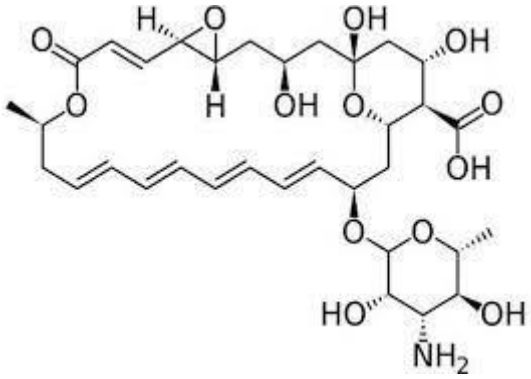
Mechanism of action

Like amphotericin B and natamycin, **nystatin** is an ionophore. It binds to ergosterol, a major component of the fungal cell membrane. When present in sufficient concentrations, it forms pores in the membrane that lead to K^+ leakage, acidification, and death of the fungus.



3. Natamycin

Natamycin inhibits the growth of fungi by specifically binding to ergosterol present in fungal cell membranes. **Natamycin** inhibits amino acid and glucose transport proteins leading to a loss of nutrient transport across the plasma membrane.



USES

Natamycin is used to treat fungal infections, including Candida, Aspergillus, Cephalosporium, Fusarium, and Penicillium. It is applied topically as a cream, in eye drops, or (for oral infections) in a lozenge.

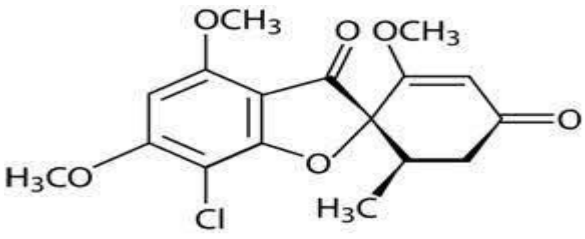
Natamycin shows negligible absorption into the body when administered in these ways.

When taken orally, little or none is absorbed from the gastrointestinal tract, making it inappropriate for systemic infections.

Natamycin lozenges are also prescribed to treat yeast infections and oral thrush.

4. Griseofulvin

Griseofulvin is fungistatic; however the exact mechanism by which it inhibits the growth of dermatophytes is not clear. It is thought to inhibit fungal cell mitosis and nuclear acid synthesis. It also binds to and interferes with the function of spindle and cytoplasmic microtubules by binding to alpha and beta tubulin.



USES

- **Griseofulvin** is **used** to treat skin infections such as jock itch, athlete's foot, and ringworm; and fungal infections of the scalp, fingernails, and toenails.
- This medication is sometimes prescribed for other **uses**; ask your doctor or pharmacist for more information.

Synthetic Antifungal Agents

The allylamines (terbinafine and naftifine) are **synthetic antifungal agents** that are effective in the topical and oral treatment of dermatophytes (fungi that infect the skin and other integumentary structures). Like the azoles, the allylamines act through inhibition of fungal ergosterol biosynthesis.

Classification of drugs

Anti fungal Antibiotics:

Polyenes: Amphotericin B (Fungizone),
Nystatin (Mycostatin)

Others: Griseofulvin

Azole Derivatives:

a) Imidazoles

Clotrimazole Econazole Fenticonazole, Ketoconazole, Luliconazole, Miconazole,Omoconazole

b)Triazoles

Albaconazole, Efinaconazole, Epoxiconazole, Fluconazole,Isavuconazole, Itraconazole, Posaconazole,

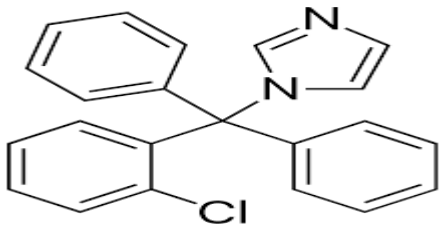
c) Thiazoles

Abafungin

MECHANISM OF ACTION

The azole **antifungal drugs** act by inhibiting the **synthesis** of the sterol components of the fungal membrane. Azoles are predominantly fungistatic. They inhibit C-14 α-demethylase (a cytochrome P450 [CYP450] enzyme), thereby blocking the demethylation of lanosterol to ergosterol, the principal sterol of fungal membranes.

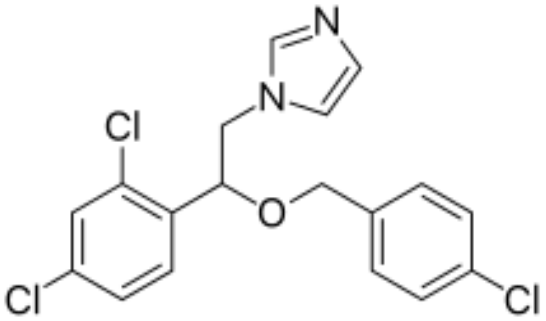
1. Clotrimazole



USES

- It is used to treat skin infections such as athlete's foot, jock itch, ringworm, and other fungal skin infections (candidiasis).
- This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arms, or legs.
- Clotrimazole is an azole antifungal that works by preventing the growth of fungus.

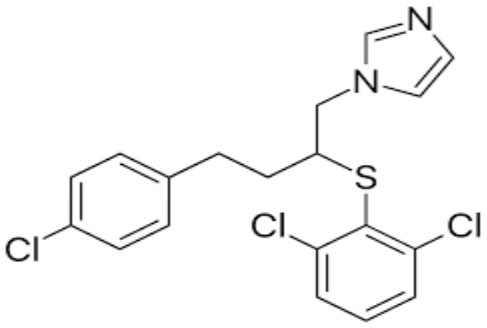
2. Econazole



USES

- It is used to treat a variety of fungal skin infections such as athlete's foot, jock itch, and ringworm.
- This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arms, or legs.
- Econazole is an azole antifungal that works by preventing the growth of fungus.

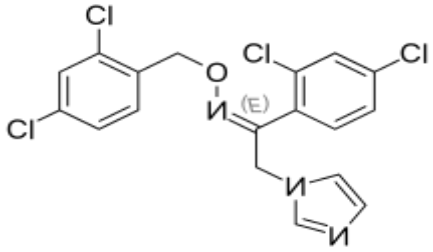
3. Butoconazole



USES

- This medication is **used** to treat vaginal yeast infections.
- **Butoconazole** reduces vaginal burning, itching, and discharge that may occur with this condition.
- This medication is an azole antifungal.
- It works by stopping the growth of yeast (fungus) that causes the infection.

4. Oxiconazole Tioconozole

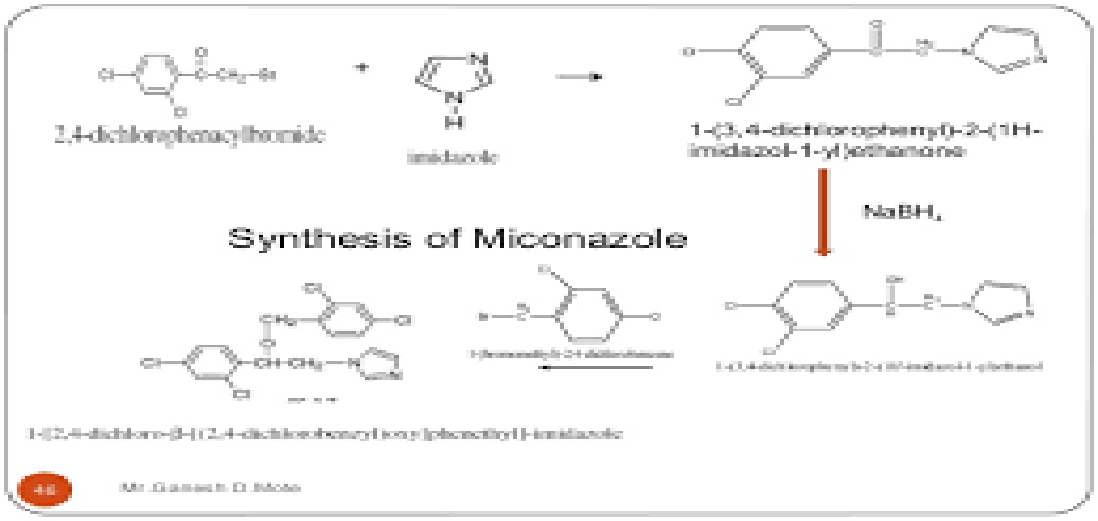


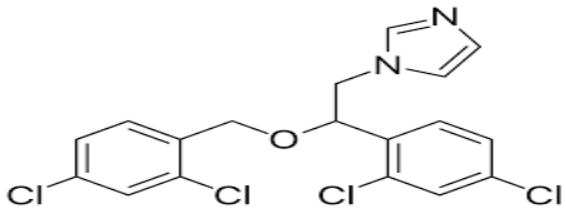
USES

- As with clotrimazole, a single **application** of **tioconazole** is effective in the management of vulvovaginal candidiasis and as a nail lacquer for fungal onychomycosis (nail infections).
- Mild to moderate vulvovaginal burning has been associated with intravaginal therapy.

5. Miconazole

Synthesis

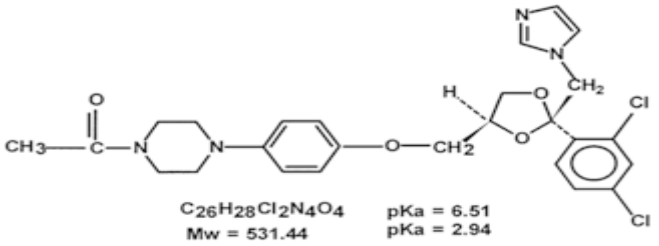




USES

Topical **miconazole** is used to treat tinea corporis (ringworm; fungal skin infection that causes a red scaly rash on different parts of the body), tinea cruris (jock itch; fungal infection of the skin in the groin or buttocks), and tinea pedis (athlete's foot; fungal infection of the skin on the feet and between the toes.

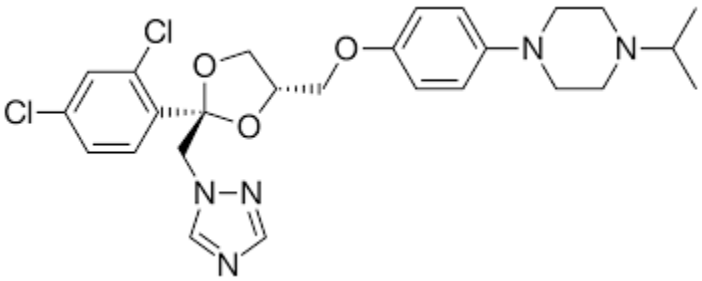
6. Ketoconazole



USES

- It is used to treat skin infections such as athlete's foot, jock itch, ringworm, and certain kinds of dandruff.
- This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arms, or legs.
- Ketoconazole is an azole antifungal that works by preventing the growth of fungus.

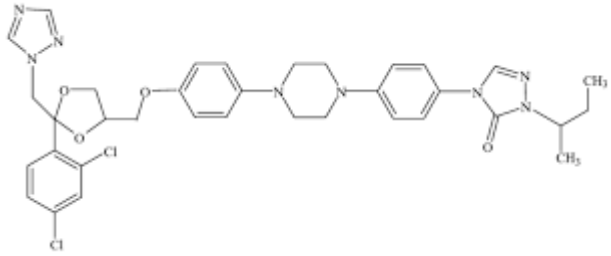
7. Terconazole



USES

- This medication is **used** to treat vaginal yeast infections.
- **Terconazole** reduces vaginal burning, itching, and discharge that may occur with this condition.
- This medication is an azole antifungal.
- It works by stopping the growth of yeast (fungus) that causes the infection.

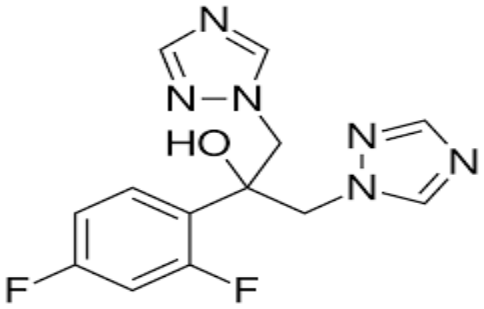
8. Itraconazole



USES

- **Itraconazole** capsules are used to treat fungal infections in the lungs that can spread throughout the body.
- **Itraconazole** capsules are also used to treat fungal infections of the fingernails.
- **Itraconazole** tablets and capsules are used to treat fungal infections of the toenails.

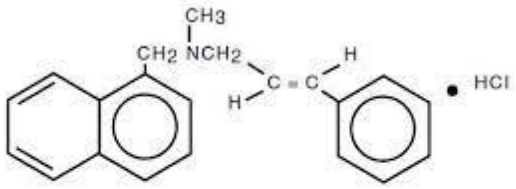
9. Fluconazole



USES

- It is used to prevent and treat a variety of fungal and yeast infections.
- It belongs to a class of drugs called azole antifungals.
- It works by stopping the growth of certain types of fungus.

10. Naftifine hydrochloride

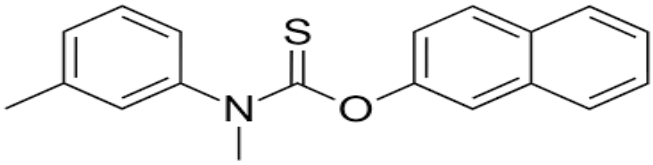


naftifine hydrochloride

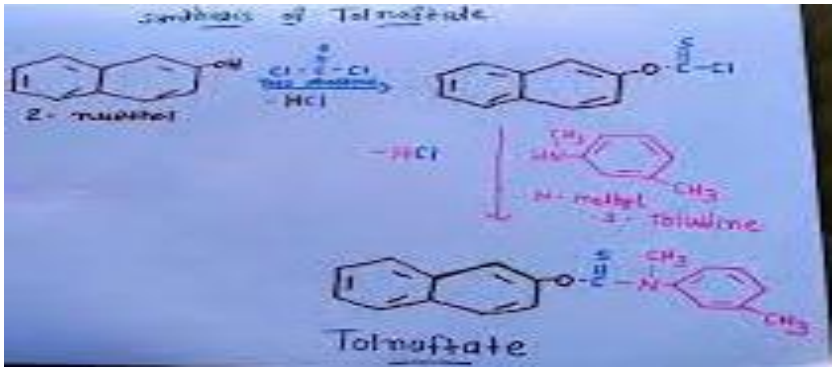
USES

- This medication is **used** to treat a variety of fungal skin infections such as ringworm, athlete's foot, and jock itch.
- **Naftifine** is an antifungal that works by preventing the growth of fungus.

11. Tolnaftate



SYNTHESIS

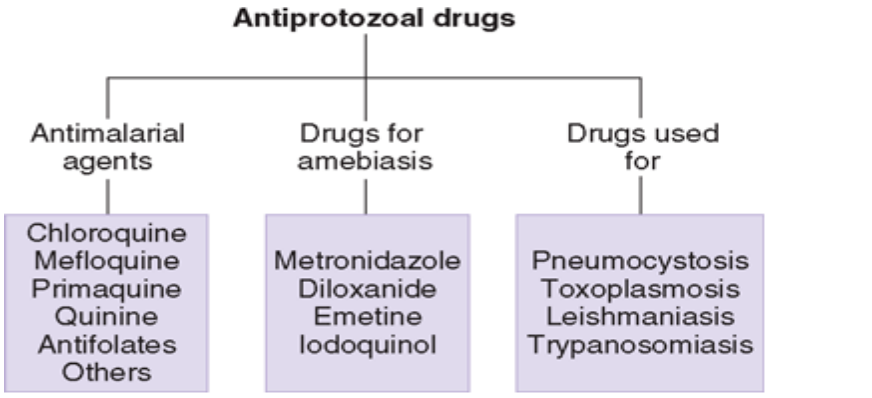


USES

- **Tolnaftate** stops the growth of fungi that cause skin infections, including athlete's foot, jock itch, and ringworm.
- This medication is sometimes prescribed for other **uses**; ask your doctor or pharmacist for more information.

ANTI-PROTOZOAL AGENTS

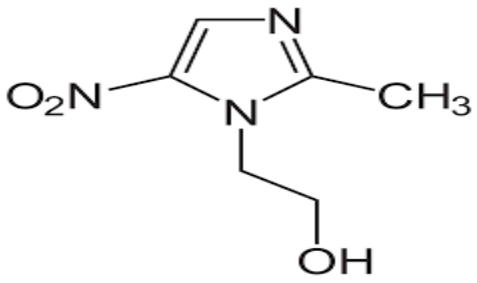
Diseases caused by protozoans constitute a worldwide health problem. This chapter concerns the drugs used to combat malaria, amebiasis, toxoplasmosis, pneumocystosis, trypanosomiasis, and leishmaniasis.



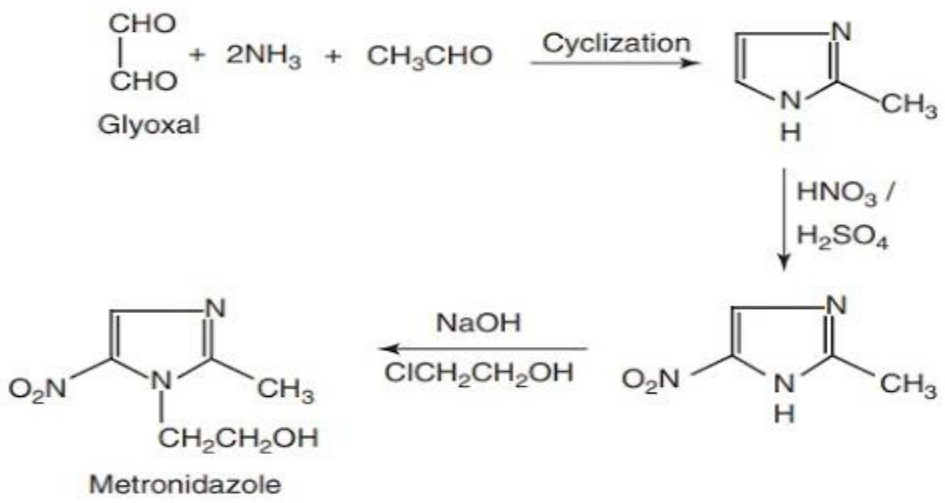
Source: Trevor AJ, Katzung BG, Kruidering-Hall M, Masters SB: *Katzung & Trevor's Pharmacology: Examination & Board Review*, 10th Edition: www.accesspharmacy.com

Malaria is one of the most common diseases worldwide and a leading cause of death. *Plasmodium* species that infect humans (*P falciparum, P malariae, P ovale, P vivax*) undergo a primary developmental stage in the liver and then parasitize erythrocytes. *P falciparum* and *P malariae* have only 1 cycle of liver cell invasion. The other species have a dormant hepatic stage responsible for recurrent infections and relapses. Primary **tissue schizonticides** (eg, primaquine) kill schizonts in the liver, whereas **blood schizonticides** (eg, chloroquine, quinine) kill these parasitic forms only in the erythrocyte. **Sporonticides** (proguanil, pyrimethamine) prevent sporogony and multiplication in the mosquito.

1. Metronidazole



Synthesis



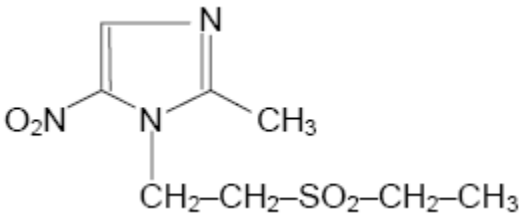
MECHANISM OF ACTION

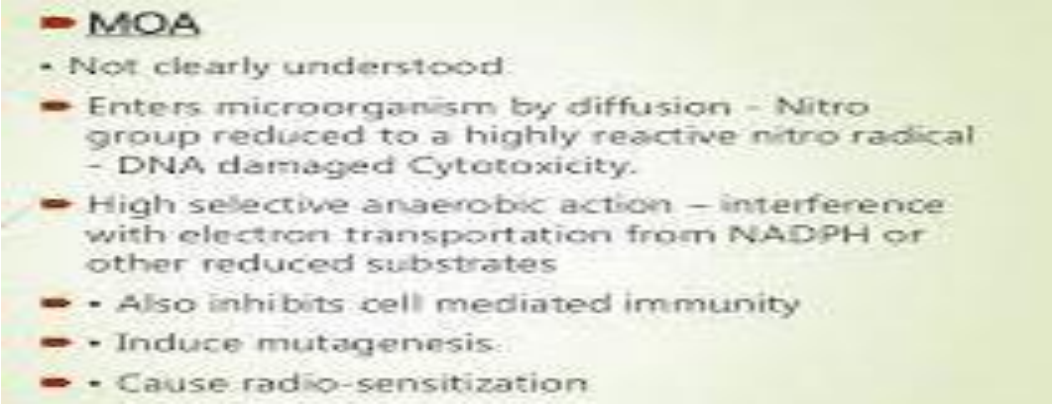
- Metronidazole acts by inhibiting nucleic acid synthesis by disrupting the DNA of microbial cells.
- This function only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic cells

USES

- It's **used** in the treatment of conditions such as bacterial vaginosis and pelvic inflammatory disease.
- It's also **used** to treat infected insect bites, skin ulcers, bed sores and wounds, and to treat and prevent bacterial and parasitic infections.
- **Metronidazole** is only available on prescription

2. Tinidazole

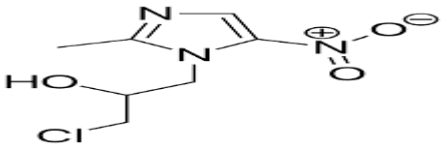


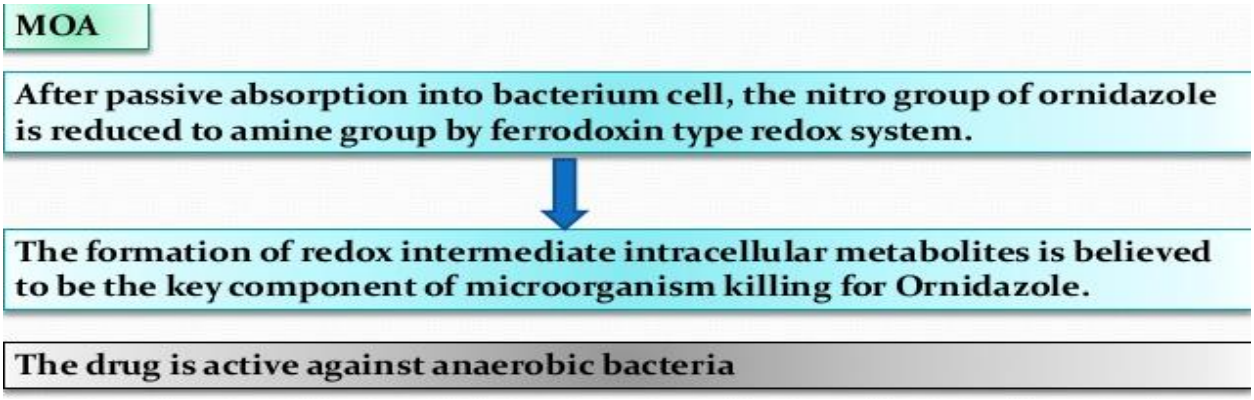


USES

- **Tinidazole** is used to treat trichomoniasis (a sexually transmitted disease that can affect men and women), giardiasis (an infection of the intestine that can cause diarrhea, gas, and stomach cramps), and amebiasis (an infection of the intestine that can cause diarrhea, gas, and stomach cramps and can spread to other.

3. Ornidazole

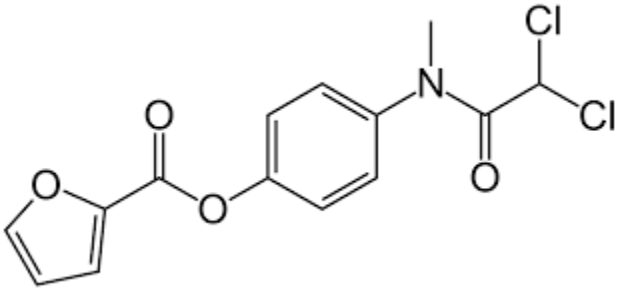




USES

- Treatment of protozoal infections such as giardiasis, trichomoniasis, etc.
- Treatment of Crohn's disease (when infection co-exists)
- To treat diarrhea, dysentery (amoebiasis), pelvic inflammatory disease.
- Prevention of infections after surgery.

4. Diloxanide

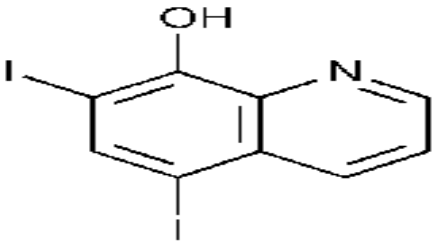


MOA of Diloxanide

- Diloxanide furoate destroys trophozoites of *E. histolytica* and prevents amoebic cyst formation. The exact mechanism of diloxanide is unknown.
- Diloxanide is structurally related to chloramphenicol and may act in a similar fashion by blocking protein synthesis.
- The prodrug, diloxanide furoate, is metabolized in the gastrointestinal tract to release the active drug, diloxanide.
- 90% of each dose is excreted in the urine and the other 10% is excreted in the feces
- Diloxanide 500 mg tid x 10d

USES

- **Diloxanide** is a medication used to treat amoeba infections.
- In places where infections are not common, it is a second line treatment after paromomycin when a person has no symptoms.
- For people who are symptomatic, it is used after treatment with metronidazole or tinidazole.
- 5. Iodoquinol



Iodoquinol:

- The mechanism of action of iodoquinol against trophozoites is unknown.

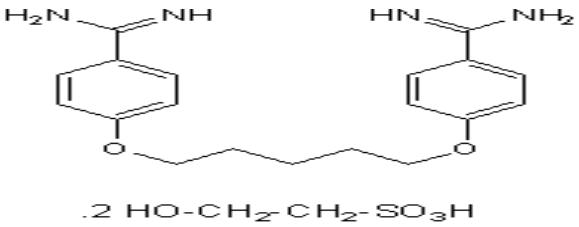
Paramomycin

- An aminoglycoside antibiotic
- Is directly amebicidal action
- Act by reducing the population of intestinal flora.

USES

- This combination medication is used to treat a variety of skin conditions (including eczema, fungal skin infections such as ringworm/athlete's foot/jock itch).
- This product contains 2 medications. **Iodoquinol** is an antibiotic that works by preventing the growth of fungus/bacteria.

6. Pentamidine Isothionate



B. Pentamidine isethionate

MOA:

- T. brucei concentrates pentamine by an energy-dependent, high affinity uptake system.
- Drug binds to parasite's DNA and interferes w/ synthesis of RNA, DNA, phospholipid and protein

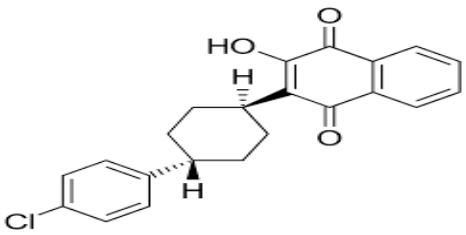
Resistance:

- Inability of trepanosome to concentrate the drug

USES

Pentamidine isethionate is **used** to prevent and treat Pneumocystis carinii pneumonia, a very serious type of pneumonia, following liver transplantation.

7. Atovaquone



Atovaquone

- For treatment and prophylaxis of malaria it has been combined with the biguanide proguanil in a fixed combination
- **MoA**:
  - Atovaquone has broad-spectrum activity against *Plasmodium* spp., *P. carinii*, *Babesia* spp., and *Toxoplasma gondii*.
  - Its mechanism of action has been most completely elucidated for *Plasmodium* spp.
  - The drug is structurally similar to the inner mitochondrial protein ubiquinone (also called coenzyme Q), which is an integral component of electron flow in aerobic respiration

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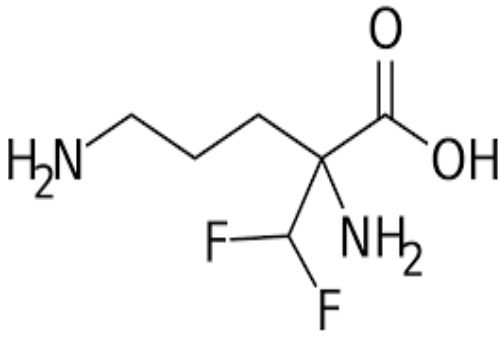
USES

Atovaquone is **used** to treat Pneumocystis jiroveci [Pneumocystis carinii] pneumonia (PCP; type of pneumonia most likely to affect people with human immunodeficiency virus [HIV]) in teenagers and adults.

Atovaquone is also **used** to prevent PCP in teenagers and adults who cannot take another medication **used** for prevention.

8. Eflornithine



MECHANISM OF ACTION

Eflornithine is a "suicide inhibitor," irreversibly binding to ornithine decarboxylase (ODC) and preventing the natural substrate ornithine from accessing the active site . Within the active site of ODC, eflornithine undergoes decarboxylation with the aid of cofactor pyridoxal 5'-phosphate (PLP). Because of its additional difluoromethyl group in comparison to ornithine, eflornithine is

able to bind to a neighboring Cys-360 residue, permanently remaining fixated within the active site.

During the reaction, eflornithine's decarboxylation mechanism is analogous to that of ornithine in the active site, where transamination occurs with PLP followed by decarboxylation. During the event of decarboxylation, the fluoride atoms attached to the additional methyl group pull the resulting negative charge from the release of carbon dioxide, causing a fluoride ion to be released. In the natural substrate of ODC, the ring of PLP accepts the electrons that result from the release of CO_2.

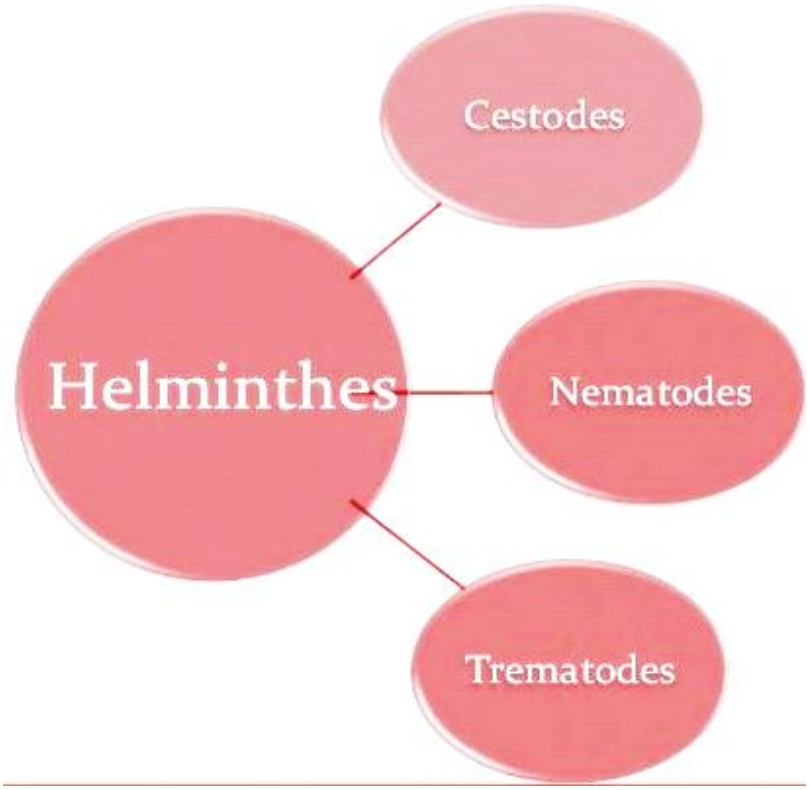
The remaining fluoride atom that resides attached to the additional methyl group creates an electrophilic carbon that is attacked by the nearby thiol group of Cys-360, allowing eflornithine to remain permanently attached to the enzyme following the release of the second fluoride atom and transimination.

USES

Sleeping sickness, or trypanosomiasis, is treated with pentamidine or suramin (depending on subspecies of parasite) delivered by intramuscular injection in the first phase of the disease, and with melarsoprol and eflornithine intravenous injection in the second phase of the disease.

Efornithine is commonly given in combination with nifurtimox, which reduces the treatment time to 7 days of eflornithine infusions plus 10 days of oral nifurtimox tablets.

ANTHELMINTICS



- Helminthiasis also known as worm infection, is any macroparasitic disease of humans and other animals in which a part of the body is infected with parasitic worms, known as helminths.

- There are numerous species of these parasites, which are broadly classified into tapeworms, flukes, and roundworms. They often live in the gastrointestinal tract of their hosts, but they may also burrow into other organs, where they induce physiological damage.

- Helminthiasis is prevalent globally about 1/3rd of world's population harbours them, but is more common in developing countries with poorer personal and environmental hygiene.

- Causative organisms harm the host by depriving him of food, causing blood loss, injury to organs, intestinal or lymphatic obstruction and by secreting toxins.

- Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths.

- The choice of drug for each worm infestation is based not only on efficacy, but also on lack of side effects/toxicity, ease of administration (preferably single dose) and low cost.

- Development of resistance has not been a problem in the clinical use of anthelmintics.

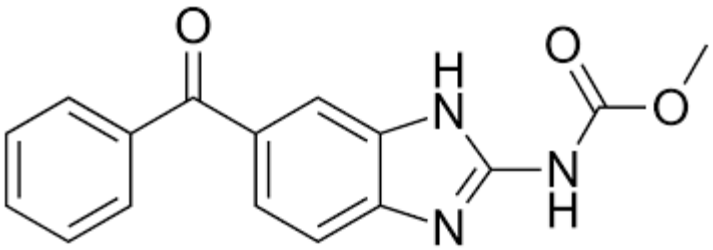
Classification of Anthelmintic Drugs

- The most commonly used Anthelmintic drugs are as follows:

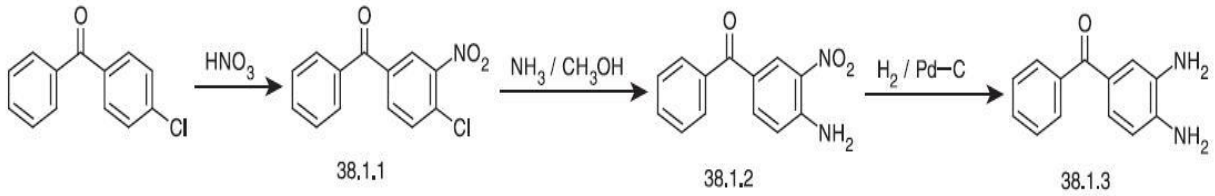
- Mebendazole
- Albendazole
- Tribendazole
- Pyrantel Pamoate
- Piperazine
- Diethyl Carbamazine Citrate
- Lvermectin

DRUGS

1. **Mebendazole**



SYNTHESIS



MOA:-

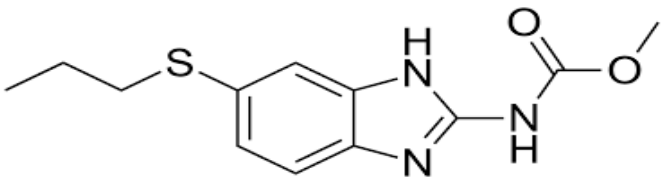
- The site of action of Mebendazole is the microtubular protein 'β-tubulin' of the parasite. It binds to β-tubulin of susceptible worms with high affinity and inhibits its polymerization. Intracellular microtubules in the cells of the worm are gradually lost.

- In addition, it probably blocks glucose uptake in the parasite and depletes its glycogen stores.

USES

- **Mebendazole** is **used** to treat several types of worm infections.
- **Mebendazole** (Vermox) is **used** to treat roundworm and whipworm infections.
- **Mebendazole** (Emverm) is **used** to treat pinworm, whipworm, roundworm, and hookworm infections.

2. Albendazole



- MOA-
- The mechanism of action of Albendazole is similar to that of Mebendazole.

❖ Pharmacokinetics-

❖ Absorption of Albendazole after oral administration is significant, but inconsistent. It is enhanced when the drug is taken with fatty meal.

❖ The fraction absorbed is converted by first pass metabolism to its sulfoxide metabolite which has potent anthelmintic action.

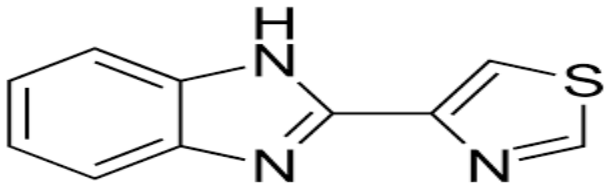
USES

Albendazole is an anthelmintic (an-thel-MIN-tik) or anti-worm medication.

It prevents newly hatched insect larvae (worms) from growing or multiplying in your body.

Albendazole is **used** to treat certain infections caused by worms such as pork tapeworm and dog tapeworm.

3. Thiabendazole



❖ It was the first benzimidazole polyanthelmintic introduced in 1961, which covered practically all species of nematodes infesting the g.i.t.— roundworm, hookworm, pin worm.

❖ MOA-

❖ It also inhibits development of the eggs of worms & kills larvae. It has antiinflammatory action as well.

❖ Pharmacokinetics-

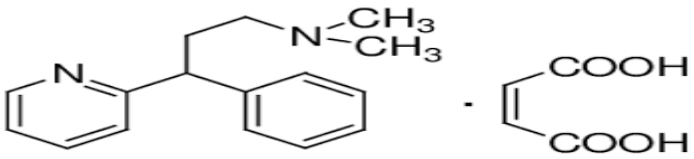
❖ Since thiabendazole is well absorbed from g.i.t., systemic adverse effects are common.

USES

- **Thiabendazole** is **used** to treat infections caused by worms such as threadworm.

- **Thiabendazole** may also be **used** to treat pinworm (when it occurs with threadworm), hookworm, whipworm, roundworm, and trichinosis.
- **Thiabendazole** may also be **used** for purposes other than those listed in this medication guide.

4. Diethylcarbamazine citrate



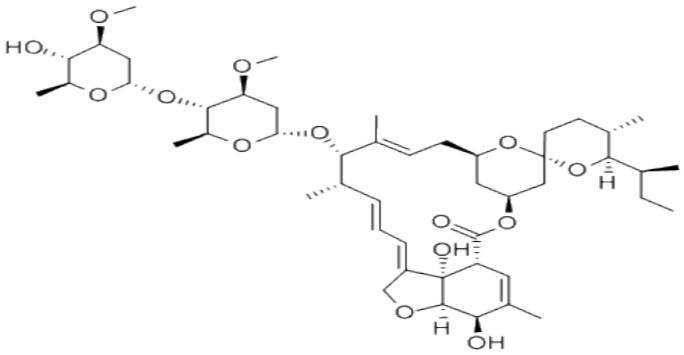
- Developed in 1948, it is the first drug for filariasis caused by the nematodes Wuchereria bancrofti (90% cases) & Brugia malayi.

- MOA-
- Diethylcarbamazine is microfilaricidal. It has a highly selective effect on microfilariae (Mf). A dose of 2 mg/kg TDS clears Mf of W. bancrofti and B. malayi from peripheral blood in 7 days. The most important action of DEC appears to be alteration of organelle membranes of the Mf promoting cell death.

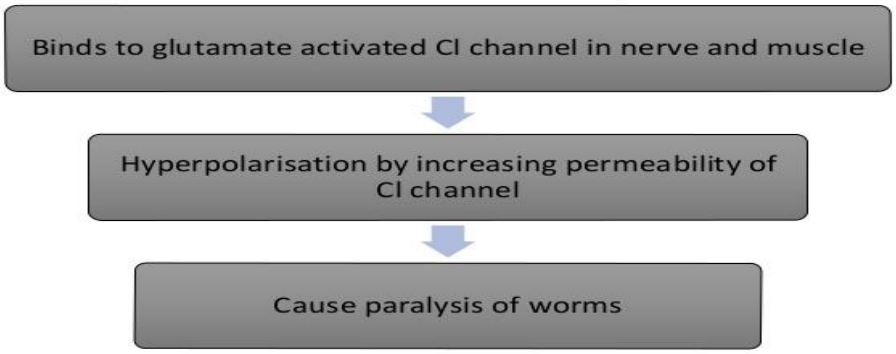
USES

Diethylcarbamazine is **used** to treat certain parasitic diseases caused by infection with roundworms of the Filarioidea type, including lymphatic filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori; tropical pulmonary eosinophilia; and loiasis.

5. Ivermectin



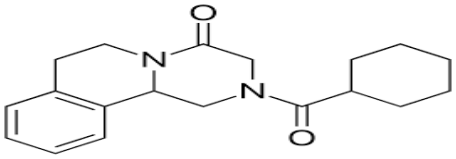
MOA:



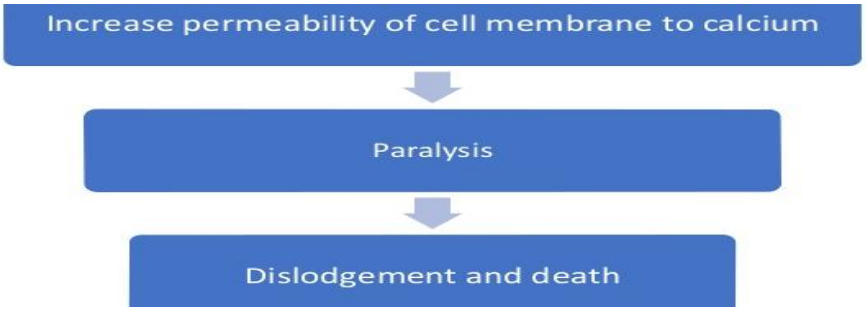
USES

- This medication is used to treat certain parasitic roundworm infections.
- Curing parasitic infections helps to improve your quality of life.
- In people with weakened defense (immune) systems, curing roundworm infections can reduce the risk of developing a severe or life-threatening infection.
- Ivermectin belongs to a class of drugs known as antihelmintics.
- It works by paralyzing and killing parasites.

6. Praziquantal



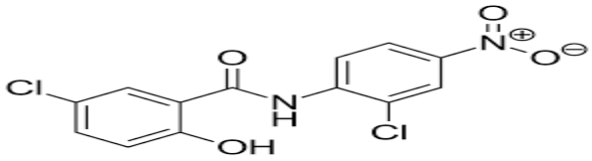
MOA:-



USES

- **Praziquantel** is **used** to treat schistosoma (infection with a type of worm that lives in the bloodstream) and liver fluke (infection with a type of worm that lives in or near the liver).
- **Praziquantel** is in a class of medications called anthelmintics.
- It works by killing the worms.

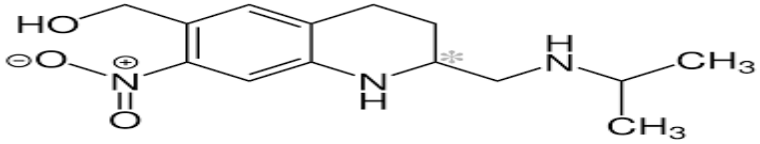
7. Niclosamide



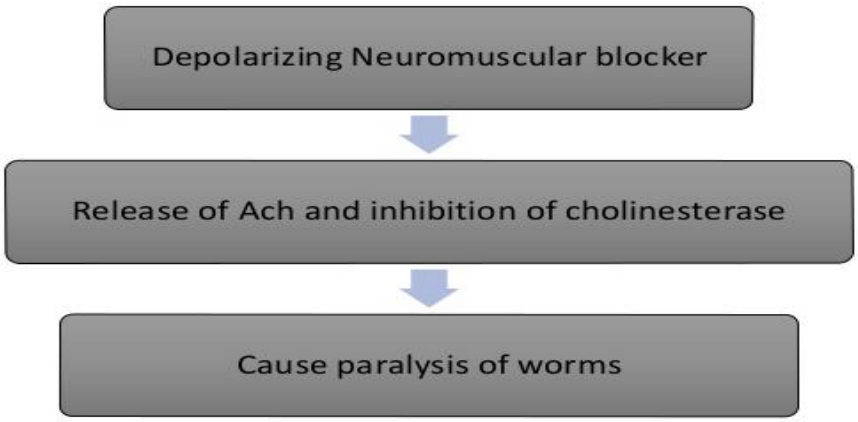
USES

- **Niclosamide** is **used** to treat broad or fish tapeworm, dwarf tapeworm, and beef tapeworm infections.
- **Niclosamide** may also be **used** for other tapeworm infections as determined by your doctor.
- It will not work for other types of worm infections (for example, pinworms or roundworms).

8. Oxamniquine



MOA:-



USES

- **Oxamniquine** is an "antihelmintic," or anti-worm, medication. It prevents worms from growing or multiplying in your body.
- **Oxamniquine** is used only to treat infections caused by the worm Schistosoma mansoni.
- This is an uncommon infection usually acquired through contact with freshwater in Africa.

SULPHONAMIDES

Sulfonamide is a functional group (a part of a molecule) that is the basis of several groups of drugs, which are called **sulphonamides**, **sulfa drugs** or **sulpha drugs**. The original antibacterial sulfonamides are synthetic (nonantibiotic) antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based upon the antibacterial sulfonamides.

Allergies to sulfonamides are common. The overall incidence of adverse drug reactions to sulfa antibiotics is approximately 3%, close to penicillin;[3] hence medications containing sulfonamides are prescribed carefully.

Sulfonamide drugs were the first broadly effective antibacterials to be used systemically, and paved the way for the antibiotic revolution in medicine.

History of Sulphonamides

Sulfonamide drugs were the first broadly effective antibacterials to be used systemically, and paved the way for the antibiotic revolution in medicine. The first sulfonamide, trade-named Prontosil, was a prodrug. Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, at that time a component of the huge German chemical trust IG Farben. The Bayer team believed that coal-tar dyes which are able to bind preferentially to bacteria and parasites might be used to attack harmful organisms in the body. After years of fruitless trial-and-error work on hundreds of dyes, a team led by physician/researcher Gerhard Domagk[6] (working under the general direction of IG Farben executive Heinrich Hörlein) finally found one that worked: a red dye synthesized by Bayer chemist Josef Klarer that had remarkable effects on stopping some bacterial infections in mice. The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch.

Prontosil, as Bayer named the new drug, was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body. It had a strong protective action against infections caused by streptococci, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other cocci. However, it had no effect at all in the test tube, exerting its antibacterial action only in live animals. Later, it was

discovered by Daniel Bovet, Federico Nitti, and Jacques and Thérèse Tréfouël, a French research team led by Ernest Fourneau at the Pasteur Institute, that the drug was metabolized into two pieces inside the body, releasing from the inactive dye portion a smaller, colorless, active compound called sulfanilamide. The discovery helped establish the concept of "bioactivation" and dashed the German corporation's dreams of enormous profit; the active molecule sulfanilamide (or sulfa) had first been synthesized in 1906 and was widely used in the dye-making industry; its patent had since expired and the drug was available to anyone.

The result was a sulfa craze. For several years in the late 1930s, hundreds of manufacturers produced tens of thousands of tons of myriad forms of sulfa. This and nonexistent testing requirements led to the elixir sulfanilamide disaster in the fall of 1937, during which at least 100 people were poisoned with diethylene glycol. This led to the passage of the Federal Food, Drug, and Cosmetic Act in 1938 in the United States. As the first and only effective broad-spectrum antibiotic available in the years before penicillin, sulfa drugs continued to thrive through the early years of World War II. They are credited with saving the lives of tens of thousands of patients, including Franklin Delano Roosevelt Jr. (son of US President Franklin Delano Roosevelt) and Winston Churchill. Sulfa had a central role in preventing wound infections during the war. American soldiers were issued a first-aid kit containing sulfa pills and powder and were told to sprinkle it on any open wound.

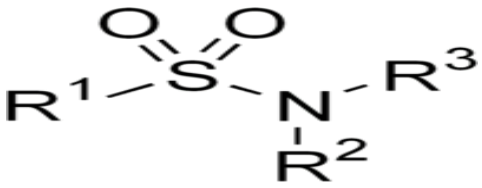
The sulfanilamide compound is more active in the protonated form. The drug has very low solubility and sometimes can crystallize in the kidneys, due to its first pK_a of around 10. This is a very painful experience, so patients are told to take the medication with copious amounts of water. Newer analogous compounds prevent this complication because they have a lower pK_a, around 5–6, making them more likely to remain in a soluble form.

Many thousands of molecules containing the sulfanilamide structure have been created since its discovery (by one account, over 5,400 permutations by 1945), yielding improved formulations with greater effectiveness and less toxicity. Sulfa drugs are still widely used for conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics.

Chemistry of Sulphonamides

In chemistry, the **sulfonamide** functional group (also spelled **sulphonamide**) is $-S(=O)_2-NH_2$, a sulfonyl group connected to an amine group. Relatively speaking this group is unreactive. The amine center is no longer basic. The S-N bond is cleaved only with difficulty. Because of the rigidity of the functional group, sulfonamides are typically crystalline. For this reason, the formation of a sulfonamide is a classic method to convert an amine into a crystalline derivative which can be identified by its melting point. Many important drugs contain the sulfonamide group.

A sulfonamide (compound) is a compound that contains this group. The general formula is RSO_2NH_2, where R is some organic group. For example, "methanesulfonamide" is $CH_3SO_2NH_2$. Any sulfonamide can be considered as derived from a sulfonic acid by replacing a hydroxyl group with an amine group. In medicine, the term "sulfonamide" is sometimes used as a synonym for sulfa drug, a derivative or variation of sulfanilamide. The first sulfonamide was discovered in Germany in 1932.



SYNTHESIS

Sulfonamides can be prepared in the laboratory in many ways. The classic approach entails the reaction of sulfonyl chlorides with an amine.

$$RSO_2Cl + R_2NH \rightarrow RSO_2NR_2 + HCl$$

A base such as pyridine is typically added to absorb the HCl that is generated. Illustrative is the synthesis of sulfonylmethylamide. A readily available sulfonyl chloride source is tosyl chloride. The reaction of primary and secondary amines with benzenesulfonyl chloride is the basis of the Hinsberg reaction, a method for detecting primary and secondary amines.

- **Sultams** are cyclic sulfonamides. Bioactive sultams include the antiinflammatory ampiroxicam and the anticonvulsant sultiame. Sultams are prepared analogously to other sulfonamides, allowing for the fact that sulfonic acids are deprotonated by amines. They are often prepared by one-pot oxidation of disulfides or thiols linked to amines. An alternative synthesis of sultams involves initial preparation of

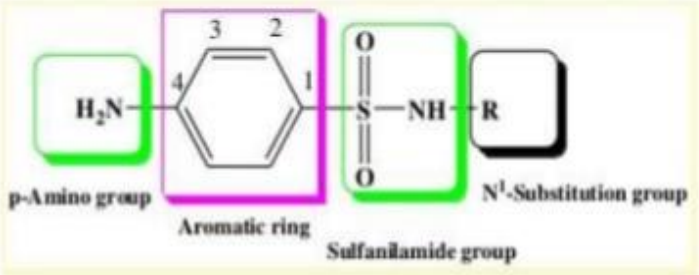
a linear sulfonamide, followed by intramolecular C-C bond formation (i.e. cyclization), a strategy that was used in the synthesis of a sultam-based deep-blue emitter for organic electronics.

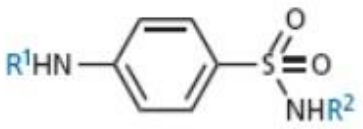
- The related sulfinamides (R(S=O) NHR) are amides of sulfinic acids (R(S=O)OH) . Chiral sulfinamides such as tert-butanesulfinamide, p-toluenesulfinamide and 2,4,6-trimethylbenzenesulfinamide are relevant to asymmetric synthesis.
- Bis (trifluoromethanesulfonyl) aniline is a source of the triflyl ($CF_3SO_2^+$) group.
- The **disulfonimides** are of the type R-S(=O)$_2$-N(H)-S(=O)$_2$-R' with two sulfonyl groups flanking an amine. As with sulfinamides this class of compounds is used as catalysts in enantioselective synthesis.

CLASIFICATION OF SULFONAMIDE

- **Short acting:** Sulfadiazine, Sulfadimidine, Sulfacetamide
- **Intermediate acting:** Sulfamethoxazole
- **Long acting:** Sulfadoxine, Sulfamethoxypyrazine, Sulfadimethoxine etc.
- **Topically used:** Mafenide, Silver sulfadiazine and Sulfacetamide
- **Ulcerative colitis:** Sulfasalazine

SAR

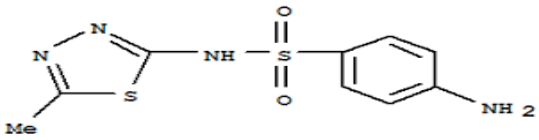




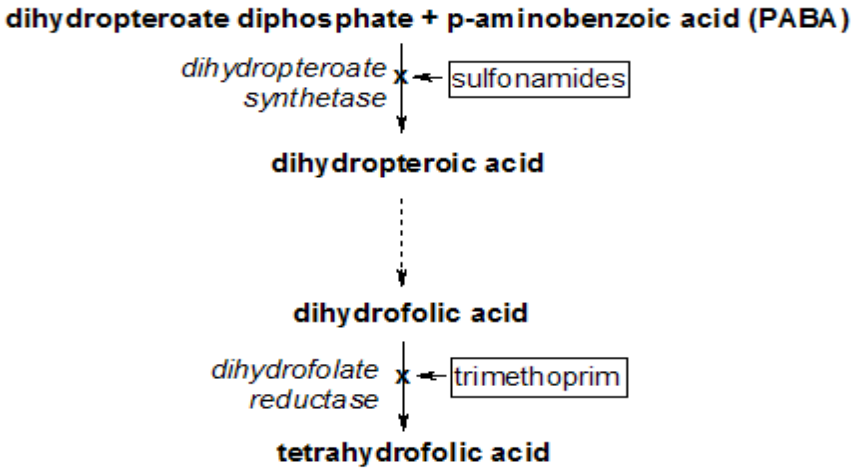
1. *Para -amino group : This is essential for activity and* must be unsubstituted The only exception is when R1 = acyl (i.e. amides).
2. The aromatic ring and the sulphonamide functional group are both required and both must be directly attached to the aromatic ring;
3. The aromatic ring must be *para -substituted only.*
4. *T*he sulphonamide nitrogen must be primary or secondary.
5. **R2 is the only possible site that can be varied in sulphonamides.**

DRUGS:-

1. **Sulphamethizole**



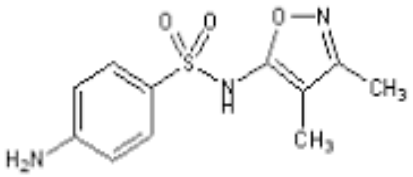
Mechanism of Action



USES:-

Sulphamethizole remains a useful drug for most uncomplicated domiciliary urinary tract infections.

2. **Sulfisoxazole**



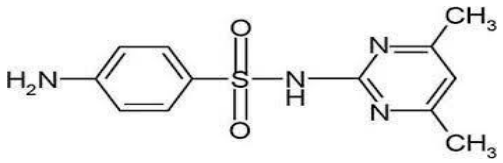
MOA:

- In human, the cell synthesized tetrahydrofolate from folic acid that obtained from food sources. This folic acid is normally transported to inside the cell by special transport system.
- Bacterial cell does not have such transport system and they should synthesize tetrahydrofolate using PABA.
- For that reason, human cells do not need dihydropteroate synthetaze enzyme which means sulfonamides have selective antibacterial activity.

USES

- **Sulfisoxazole** is **used** to treat or prevent infections in many different parts of the body.
- It belongs to the group of medicines known as sulfonamide antibiotics.
- It works by preventing the growth of bacteria. However, this medicine will not work for colds, flu, or other virus infections.

3. Sulphamethizine



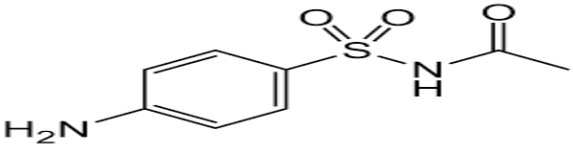
Mechanism of action

Sulfamethazine is a sulfonamide drug that inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA) for binding to dihydropteroate synthetase (dihydrofolate synthetase).

USES

- **Sulfamethazine** is an antibacterial agent **used** in the treatment of various bacterial infections, such as bronchitis, prostatitis, and urinary tract infections.
- A sulfanilamide anti-infective agent.
- It has a spectrum of antimicrobial action similar to other sulfonamides.

4. Sulfacetamide



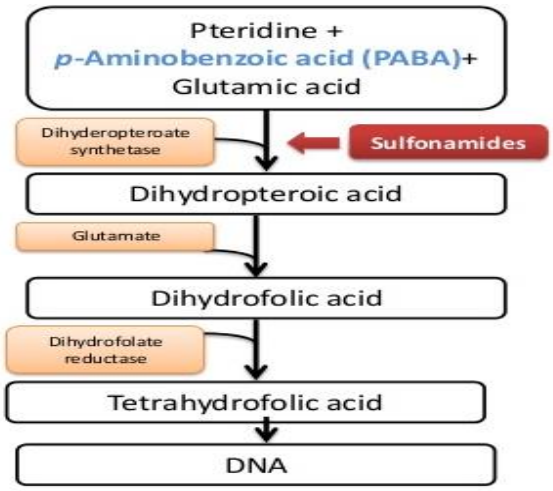
MOA:

Bacteria synthesize their own folic acid (FA) of which *p*-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium.

Sulfonamides, are structural analogues of PABA, inhibit bacterial folate synthase and formation of folate get inhibited.

Sulfonamides competitively inhibit the PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid.

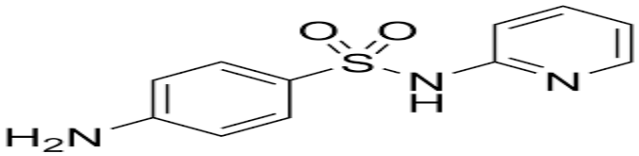
Sulfonamide altered folate an which is metabolically injurious



USES

- Ophthalmic **sulfacetamide** stops the growth of bacteria that cause certain eye infections. It is **used** to treat eye infections and to prevent them after injuries.

5. Sulphapyridine



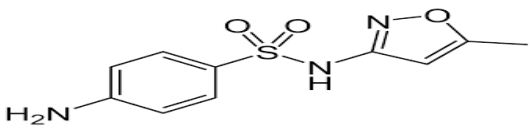
Mechanism of action

Their antibacterial **action** is inhibited by pus. **Sulfapyridine** is a competitive inhibitor of the bacterial enzyme dihydropteroate synthetase. The inhibited reaction is necessary in these organisms for the synthesis of folic acid by means of processing the substrate para-aminobenzoic acid (PABA).

USES

Sulfapyridine is a sulfa medicine. It is **used** to help control dermatitis herpetiformis (Duhring's disease), a skin problem. It may also be **used** for other problems as determined by your doctor. However, this medicine will not work for any kind of infection as other sulfa medicines do.

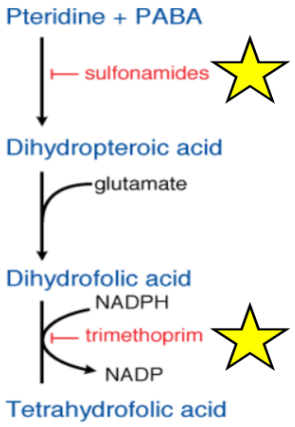
6. Sulfamethoxaole



MOA:

ONE-TWO PUNCH!

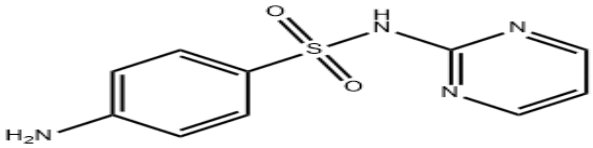
- Sulfonamide (SMX) – inhibits incorporation of PABA
- Trimethoprim (TMP) – prevents reduction of dihydrofolate
- Optimal dose ratio
  - 20:1 (SMX:TMP)



USES

- **Sulfamethoxazole** and trimethoprim combination is **used** to treat infections including urinary tract infections, middle ear infections (otitis media), bronchitis, traveler's diarrhea, and shigellosis (bacillary dysentery).

7. Sulphadiazine



Mechanism of action

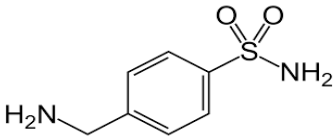
Sulfadiazine is a competitive inhibitor of the bacterial enzyme dihydropteroate synthetase. This enzyme is needed for the proper processing of para-aminobenzoic acid (PABA) which is essential for folic acid synthesis. The inhibited reaction is necessary in these organisms for the synthesis of folic acid.

USES

Sulfadiazine is an antibacterial prescription medicine approved by the U.S. Food and Drug Administration (FDA) for the prevention and treatment of certain types of bacterial infections,

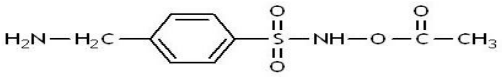
including the treatment of chancroid, Toxoplasma gondii encephalitis, urinary tract infections, and other infections.

8. Mefenide acetate



Mechanism of action

Mafenide acetate (Sulfamylon®)



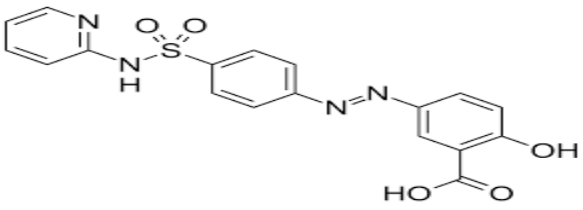
4-(Aminomethyl)benzenesulfonamide

- Not true sulfanilamide compound
- Not inhibited by PABA [its M.O.A. involves different mechanism than true sulfonamides].
- Effective ≠ *Clostridium welchii* in topical use for infected wounds.
- Not effective orally.
- Used alone or with antibiotics in treatment of slow healing infected wounds.
- If used in large quantities → metabolic acidosis. So, a series of new organic salts was prepared.
- The acetate derivative in ointment base is the most efficient.

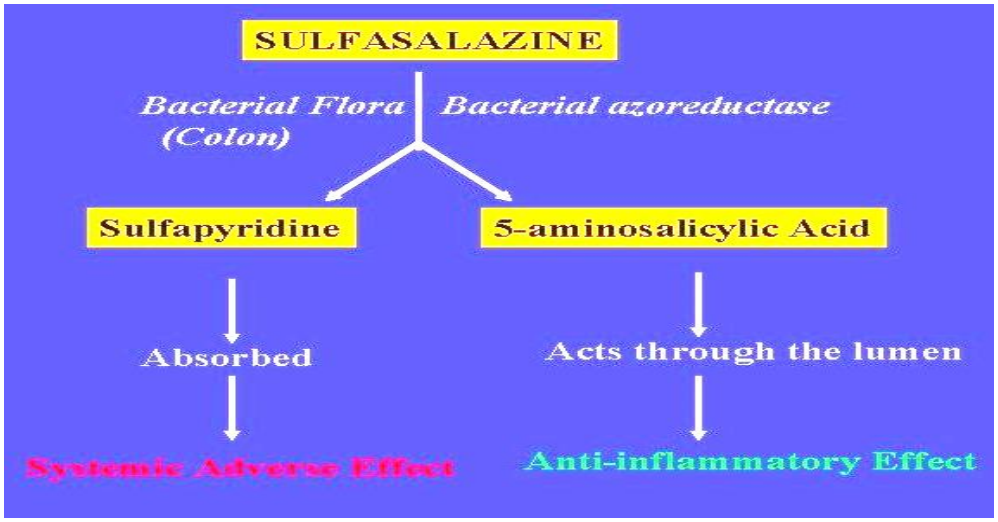
USES

- This medication is used alone or with other medications to help prevent and treat wound infections in patients with severe burns.
- **Mafenide** is a drug applied to the skin that belongs to a class of drugs known as sulfa antibiotics.
- It works by killing bacteria that may infect an open wound.

9. Sulfasalazine



Mechanism of action



USES

- **Sulfasalazine** is **used** to treat bowel inflammation, diarrhea (stool frequency), rectal bleeding, and abdominal pain in patients with ulcerative colitis, a condition in which the bowel is inflamed.

IMPORTANT QUESTIONS

Very Short Answer Type Questions

Q1 Amphotericin B is not effective for which fungal disease.

Q2 Griseofulvin is indicated for?

Q3 Clotrimazole is used for the conditions except?

Q4 Metronidazole is selectively active against anaerobic organisms?

Q5 Tinidazole differs from Metronidazole in that?

Q6 In addition to amoebiasis, Metronidazole is used for?

Q7 Anthelmintic action of Piperazine is due to?

Q8 Piperazine antagonises the anthelmintic action of which drug?

Q10 Thiabendazole is rarely used now because?

Q11 which drug is effective in filariasis?

Q12 which sulfonamide is not used in diuretics?

Q13 Sulfonamides are metabolized by humans principally by?

Q14 which is the major side effect of sulfonamide?

Short Answer Type Questions

Q15 what are antifungal agents?

Q16 Explain general mechanism of action of antifungal agents.

Q17 Write a note on antifungal antibiotics.

Q.18 what are synthetic antifungal agents?

Q19 what are protozoa?

Q20 Classify antiprotozoal agents?

Q21 Write down the structure & uses of

a) Tinidazole

b) Pentamidine

c) Iodoquinol

Q22 what are helminths?

Q.23 what are anthelmintics? Give its classification,

Q24 Write down the structure and uses of a) Praziquantal b) Thiabendazole c) Mebendazole

Q25 Explain mechanism of action of Anthelmintics.

Q26 what is the basic structure of sulphonamides?

Q27 Write a note on historical development of sulphonamides.

Q28 what are folate reductase inhibitors? Give its mechanism of action.

Q29 Write down structure and uses of a) Dapsone b) Sulphasalazine c) Trimethoprim d) Sulphacetamide.

Q30 Explain chemistry of Sulphonamides

Long Answer Type Questions

Q.1 what are antifungal agents? Classify them. Explain any two drugs in this category.

Q.2 Write down structure, uses and mechanism of a) Econazole b) Itraconazole c) Fluconazole d) Naftifine

Q.3 Give synthesis of a) Miconazole b) Tolnaftate

Q4 Explain antiprotozoal agents giving suitable examples**.**

Q5 Classify antiprotozoal agents & explain mechanism of action of these agents.

Q6 Give structure, uses & synthesis of Metronidazole

Q7 Explain anthelmintics giving suitable examples.

Q8 Give synthesis of' a) Mebendazole b) Diethylcarbamazine citrate

Q9 Give classification, mechanism of action and uses of Anthelmintics.

Q10 Explain any two drugs of class natural products as Anthelmintics.

Q11 what are Sulphonamides? Give its classification. Explain its mechanism of action.

Q12 Explain Folate reductase inhibitors giving suitable examples.

Q13 Write down the synthesis of a) Sulphacetamide b) Dapsone c) Sulphamethoxazole d) Trimethoprim.