B.Pharmacy
Subject-Medicinal Chemistry III
Sub Code-BP601T

Anthelmintics

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Introduction

- *Anti* – against and *helminths* – worms
- May be
  - Vermicide – Drugs that kill worms
  - Vermifuge – expel infesting helminths
    - Peristaltic movement of Intestine
    - Cathartic and purgative action
- Ideal anthelmintics:
  - Orally effective
  - Effective in single dose
  - Inexpensive
  - Wide safety of margin with highest toxicity to worms, but lesser toxic to the host

Objective of the course:

Understand the importance of drug design and different techniques of drug design

Learning Outcomes:

Students will learn about the structures and MOA of antifungal,antiprotozoal agents and anthelmintics.

Students will learn about SAR of above mentioned agents.

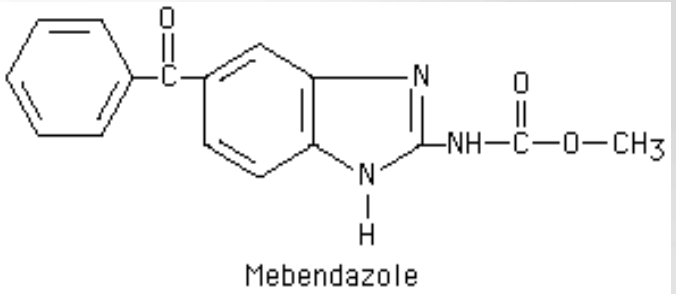
Common Helminths

- **Roundworm:** Ascaris lumbricoides
- **Hookworm:** Ancylostoma duodenale and Necater americanus
- **Threadworm:** Enterobius vermicularis and Strongyloides stercoralis
- **Whipworm:** Trichuris trichiuria and Trichinella spiralis
- **Filaria:** W. Bancrofti, Brugia malayi
- **Tapeworms:** T. saginata, T. solium, H. nana
- **Hydatid disease:** E granulosus and E multilocuralis
- **Guniea worm:** Dracunculus medinensis

Available Drugs

1) Mebendazole
2) Albendazole
3) Pyrantel pamoate
4) Piperazine
5) Levamisole and tetramisole
6) Diethyl carbamazine citrate(DEC)
7) Ivermectin
8) Niclosamide
9) Praziquantel

Mebendazole



Mebendazole

- Synthetic benzimidazole derivative
- **Action:**
  - 100% cure rate for round worm, hookworm, enterobius (less for Strongyloides) and trichuris (not for tissue Trichinella spiralis)
  - 75% effective for tape worms but not for H. nana
  - Hadatid cyst: prolonged treatment
  - Hatching of nematode eggs and larva inhibited and Ascaris eggs are killed
- **MOA:**
  - Slow in action, takes 2-3 days to develop
  - Blocks glucose uptake in the parasite and depletion of glycogen store
  - Site of action: microtubular protein "ß-tubulin" – inhibits polymerization
  - Intracellular mictotubules are grdually lost

Mebendazole – contd.

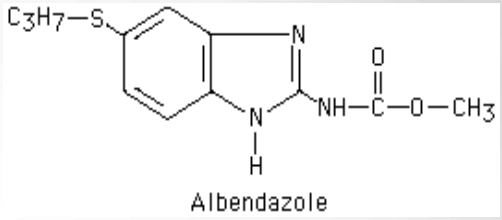
- Pharmacokinetics: Minimal absorption, 75-90% is passed unabsorbed in the faeces. Excreted mainly in urine as inactive metabolite

- **Adverse effects:**
  - No adverse effects with short term therapy, mild GIT disturbanes- nausea, diarrhoea and abdominal pain
  - Allergic reactions, granulocytopenia, loss of hair and elevation of liver enzymes
  - Enzyme inducers and inhibitors
  - Pregnancy -????

- **Uses:** Available as 100 mg chewable tablet and 100mg/ml suspension
  - Common indications: 100 mg twice daily for 3 days
  - Enterobius 100 mg single dose +repeat after 2-3 weeks
  - Trichinella spiralis – 200 mg twice daily for 4 days
  - Hydatid cyst: 200-400 mg twice daily for 3-4 weeks

} Albendazole preferred

Albendazole



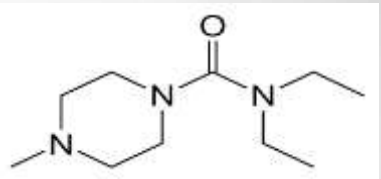
Albendazole

- Congener of Mebendazole
- **Action:** comparable efficacy with mebendazole for round worm, hook worm and enterobius
  - Less effective against trichuris
  - But, more effective against strongyloides
  - Trichinella effectiveness is almost same
  - More effective in tape worm (including H. nana) and hydatid larvae and ova of ascaris and hook worm
  - Weak microfilarial action and cutaneous larva migrans
- **Pharmacokinetics:** Moderate and inconsistentoral absorption
  - Fatty meals enhance absorption
  - Fraction absorbed is converted to "sulfoxide" metabolite – active
  - Its active and penetrates brain with t1/2 of 8-9 Hrs – **BASIS of TISSUE** Anthelmintic action
  - For intesinal worm given in empty stomach and for tissue action – with fatty meals

Albendazole – contd.

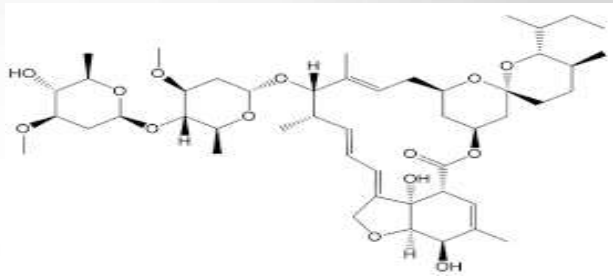
- **Uses and dosage:** Available as 400 mg tablet and 200 mg/5ml susp.
  - Normal dosing: Single dose of 400 mg (200 mg below 2 years)
  - Tape worm: 400 mg for 3days
  - Cutaneous larva migrans: treatment of choice - 400 mg for 3 days
  - Neurocysticercosis: treatment of choice – 400 mg twice daily for 1-2 weeks
  - Hydatid disease: 400 mg BD for 4 weeks, repeat after 2 weeks upto 3 courses. Treatment of choice before and after urgery
  - Filariasis: with DEC or Ivermectin – in lymphatic filariasis
  - Used in mass programmes – yearly dose for microfilaraemia transmission
  - Contraindicated in pregnancy

DIETHYLCARBAMAZINE CITRATE



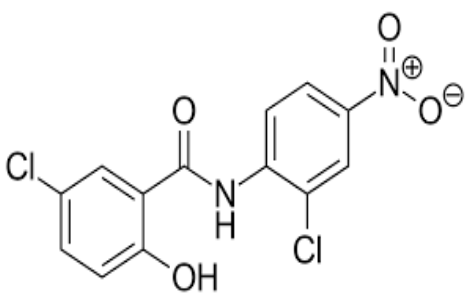
- Drug of choice for the treatment of filariasis, loiasis and tropical eosinophillia
- Pharmacokinetics:
  - It is synthetic piprazine derivative
  - Rapidly absorbed from gut
  - It has a half life of 2-3 hours which increases in alkaline urine to 10 hours
  - It is excreted in urine unchanged
  - Dosage is reduced in urinary alkalosis and renal impairment
- MOA: 2 mechanisms
  - Alteration of Mf membrane – to be readily phagocytosed by tissue monocytes
  - Since piperazine derivative – hyperpolarization and muscular weakness
- Uses: 50 mg, 100 mg tabs and susp available
  - Filariasis: 2 mg/kg tds X 7 days – improved
    - Intermittent microfilaria is problem (100 mg/kg for 3 weeks) – more than 1 course of therapy in a gap of 3-4 weeks
    - Elephantiasis not affected
  - Tropical eosinophilia (2-4 mg/kg tds for 2-3 weeks)
- ADRs: Nausea, vomiting, loss of appetite etc.
  - Febrile condition – rash, pruritus, enlargement of lymph nodes – withdraw the drug and start antihistamines and corticosteroids
  - Can be minimized by starting low dose

Ivermectin



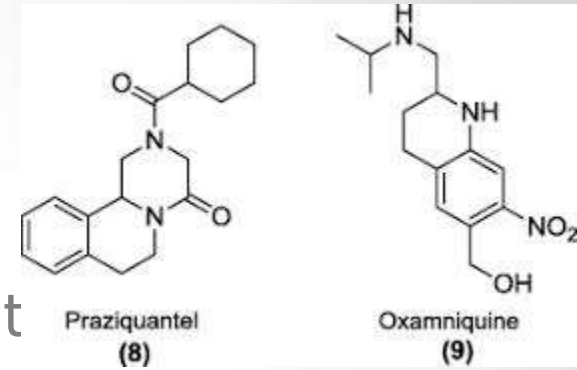
- Obtained from Streptomyces avermitilis
- Action:
  - Drug of choice for Onchocercosis volvulus and Strongyloides and equal to DEC in Filaria
  - Also efective against cutaneous larva migrans and ascariasis – also scabies and head lice
- MOA:
  - Acts via special type of glutamate gated Cl- channel found only in invertebrates
  - Such channels are absent in man, flukes and tape worms – not effective
  - Potentiation of GABA activity – paralysis of muscles of worms
- Pharmacokinetics: absorbed well orally, widely distributed but not in CNS, long half-life – 48 to 60 Hrs
- Uses: 3/6 mg tablets
  - Filaria: single dose 0.2 mg per kg with 400 mg Albendazole annually for 5-6 years
  - Strongyloides: 0.2 mg/kg single dose
  - Replaced DEC in O. volvulous by WHO
- ADRs: Pruritus, giddiness, nausea, abdominal pain and sudden ECG changes

Niclosamide



- Against tape worms – saginata, solium, latum and nana
- MOA: Inhibition of oxidative phosphorylation in mitochondria and interference of anaerobic generation of ATP
  - Injured worms are digested or expelled (purgation)
  - But, problem with T. solium – dangerous visceral cysticercosis
- Regimen: available as 0.5 gm tabs.
  1. 2 gm stat – repeat after 1 Hr and saline purgation
  2. 2 gm daily for 5 days in H. nana infestation
- ADRs: well tolerated, no systemic toxicity and can be given in pregnancy

PRAZIQUANTEL



- Novel anthelmintic with wide range of act
- Action: Mainly on Schisosomiasis and other Trematodes, cestodes but not nematodes
- MOA:
  - Rapidly taken up by worms
  - Leakage of intracellular Ca++ causing paralysis
  - Worms lose grip on intestinal wall including tissues and veins
  - Acts against all stages of worms including larvae
  - Other MOA – vacuolization of membrane and release of contents of tap worms
- Pharmacokinetics: Rapidly absorbed and enhanced by food
  - High first pass metabolism
  - Crosses BBB and attains therapeutic conc. In CSF
  - Phenytoin, carbamazepine and steroids induce metabolism – failure of therapy

Praziquantel – contd.

- ADRs: Bitter in taste, produce nausea and vomiting and abdominal pain
  - Headache, dizziness and sedation
  - Urticaria, rash, fever etc- destroyred flukes
- Uses: available as 500 mg/600 mg tabs
  - First line of drug in all tape worms except Neurocysticercosis (10-25 mg/kg per day single dose)
  - Neurocysticercosis (50-100mg/kg/day for 2 weeks)
  - First line of drug in all schistosome infestations and flikes except Fasciola hepatica (50-75 mg/kg/day)

THANK YOU

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Module 4

Anti protozoal Agents

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Protozoal Infection

- **Protozoal diseases are less easily treated than bacterial infections:**
  - Unicellular protozoal cells have metabolic processes closer to human cells than bacteria.
  - Many of antiprotozoal drugs cause serious toxic effects and most of them are not safe I n pregnancy.
- Protozoal diseases, such as:
- Malaria
- **Amebiasis**
- Leishmaniasis
- Trypanosomiasis
- Trichomoniasis
- Giardiasis

Amoeba

- *Dientamoeba fragilis*-causes Dientamoebiasis
- *Entamoeba dispar*
- *Entamoeba hartmanni*
- *Entamoeba coli*
- *Entamoeba moshkovskii*
- *Endolimax nana*
- *Iodamoeba butschii*

Amoebiasis

- Amoebiasis is caused by *E. histolytica, a protozoa* parasite
- Approximately 48 million individuals suffer from amoebiasis throughout the world.
- At least 40 thousand deaths are attributable to amoebiasis
- Ranks third among parasitic causes of deaths, behind only malaria and schistosomiasis

AMOEBIASIS (E. HISTOLYTICA)

- Trophozoites and cysts
- Trophozoites can
  - (i) Live in lumen
  - (ii) Invade colon epithelium – ulceration
  - (iii) Spread to other organs/tissues e.g. liver

Trophozoites can simply live on gut bacteria – addition of a broadspectrum antiobiotic, e.g. a Tetracycline can lead to rapid improvement as the parasites major food source is depleted

<u>Range of illness/symptoms</u>

(i) Asymptomatic carrier
(ii) Mild intestinal infection - diarrhea
(iii) Severe intestinal infection - dysentery
(iv) Amoebic liver hepatitis and abscess
(V) Amoeboma & extraintestinal infection

Clinical Classification Antiamoebic Drugs

Mixed amebicides : both systemic and luminal

- **Metronidazole**
- **Tinidazole**

Luminal amebicides

- treatment of the asymptomatic colonization state.
- **Iodoquinol,**
- **Paromomycin**
- **diloxanide furoate**

systemic amebicides

- These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebas
- **Chloroquine**
- **Emetine**
- **Dehydroemetine**

Another Classification of Antiamoebics

I. Tissue Amoebicide

A. Intestinal as well as extra intestinal amoebicide

i) Nitroimidazole derivatigves: Metronidazole, Ornidazole, Secnidazole, Tinidazole

ii) Alkaloid: Emetine and Dehydroemetine

B. Extra intestinal/hepatic amoebicide

Chloroquine

II. Luminal Amoebicide

a. Amide Derivatives: Diloxanide Furoate

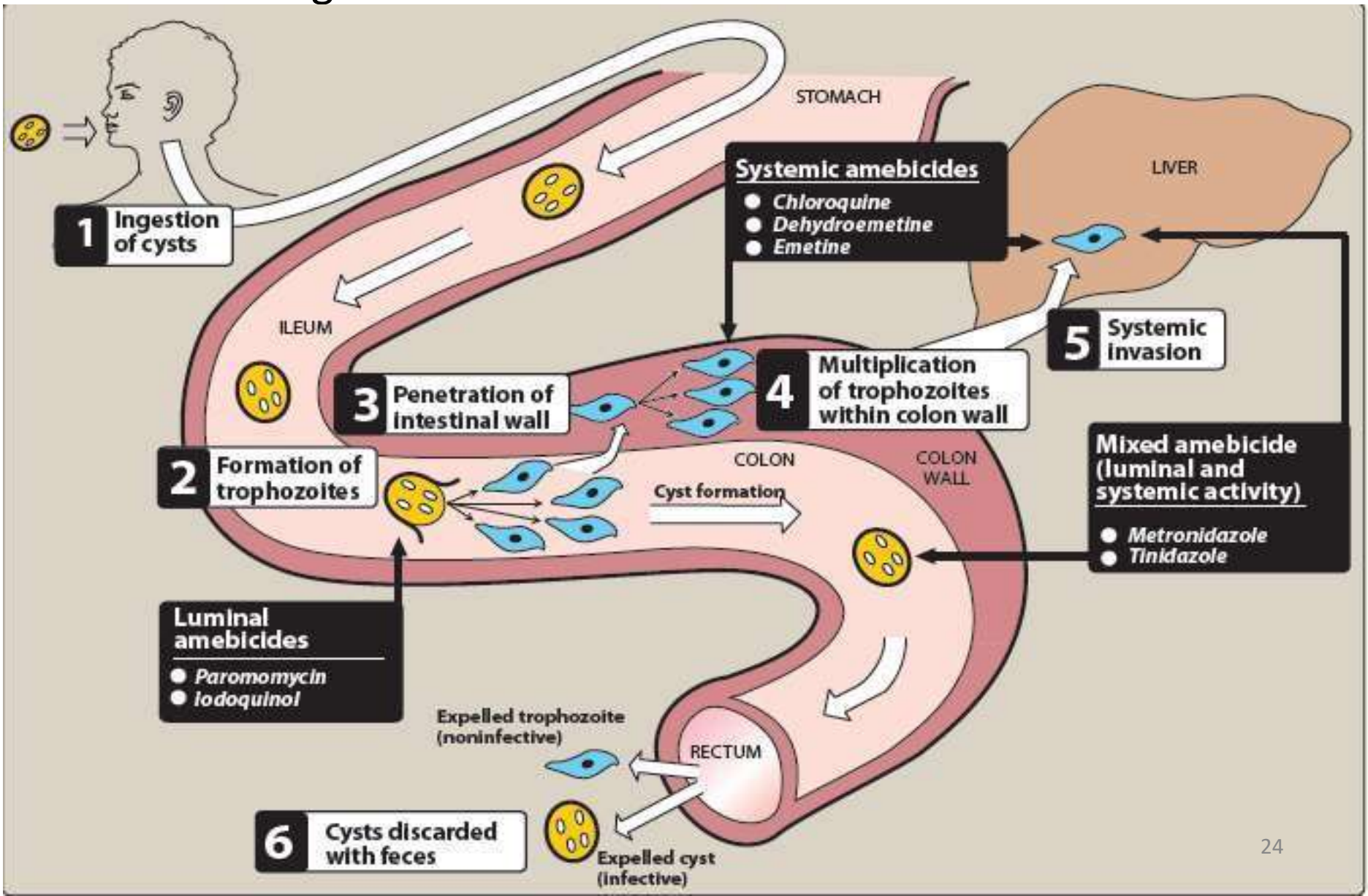
b. 8-Hyroxyquinolines: Iodoquinol, clioquinol

c. Antibiotic : Tetracycline, Pramomycin

Chemical Classification

1. Nitroimidazole derivatives: Metronidazole, Tinidazole , Ornidazole , Secnidazole
2. Dichloroacetamides: Diloxanide Furoate, Etofamide, Clefamide, Teclozan
3. Emetines: Emetine, Dehydroemetine
4. Halogenated 8 Hydroxyquinolines: Clioquinol Iodoquinol
5. 4-amino quinoline derivatives: Chloroquine
6. Antibiotics: Paromomycin, Tetracycline
7. Nitrothiazolidines: Nitazoxanide

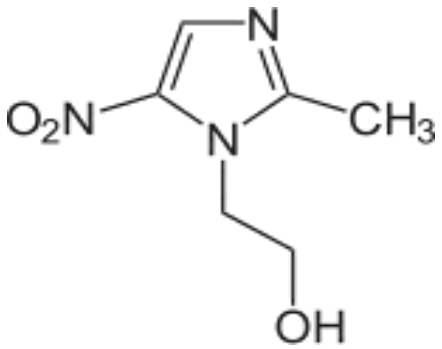
Life cycle of Entameaba histolytica and the sites of action of amebicidal drugs



1. Nitroimidazole derivatives:

   Metronidazole, Tinidazole , Ornidazole , Secnidazole

Nitroimidazoles



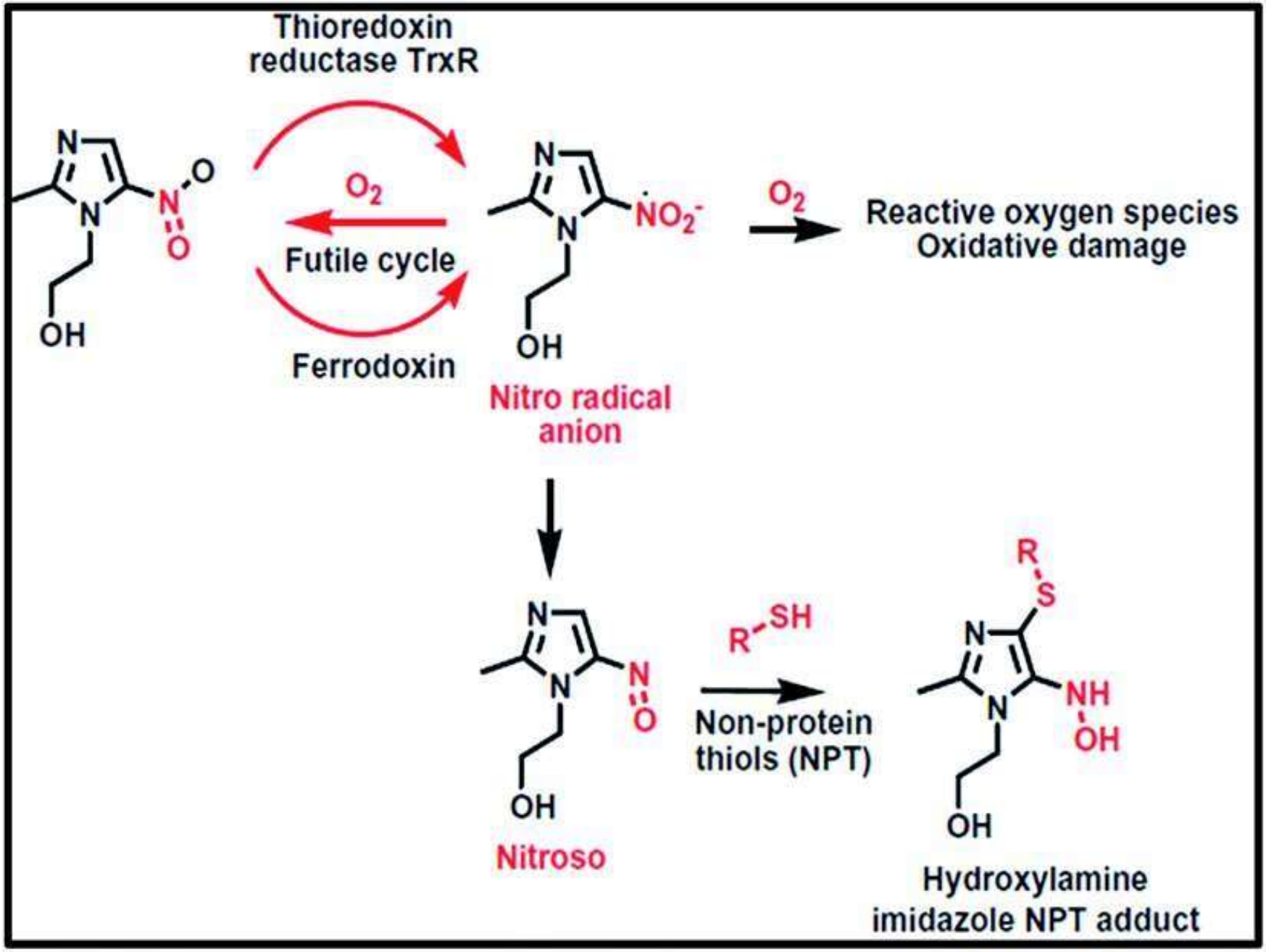
- **Metronidazole**
- **MOA:** Releases in the parasites toxic superoxide or hydroxyl radical forming reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death.
- Metronidazole is Drug of choice (DOC) for **amebic infection** and for infections caused by:
  - Giardia lamblia
  - Trichomonas vaginalis
  - Anaerobic cocci, gram+ve bacilli and "C.difficile" that cause Pseudomemberanous colitis

Metronidazole (cont.)

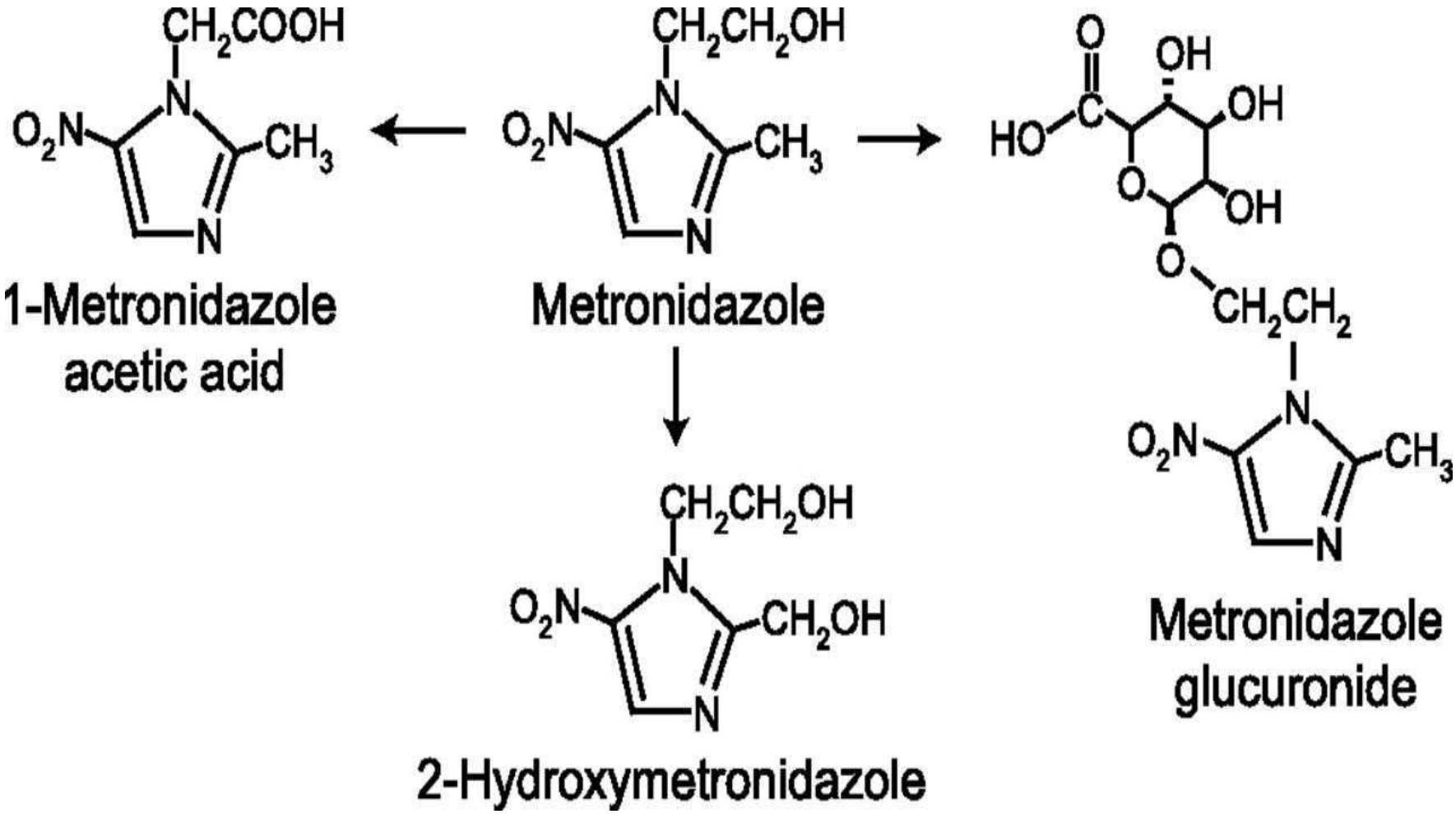
- It kills the **trophozoites** and less effective against the **cyst**
  - Most effective against the invasive amebae
  - Less effective against the luminal amebae

SO

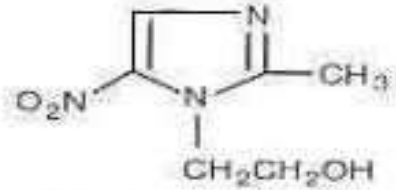
- it is usually administered with a luminal amebicide, such as ***iodoquinol*** *or* ***paromomycin***


Thioredoxin
reductase TrxR
O2
Futile cycle
Ferrodoxin
NO2-
Nitro radical
anion
O2
Reactive oxygen species
Oxidative damage
Nitroso
R-SH
Non-protein
thiols (NPT)
Hydroxylamine
imidazole NPT adduct

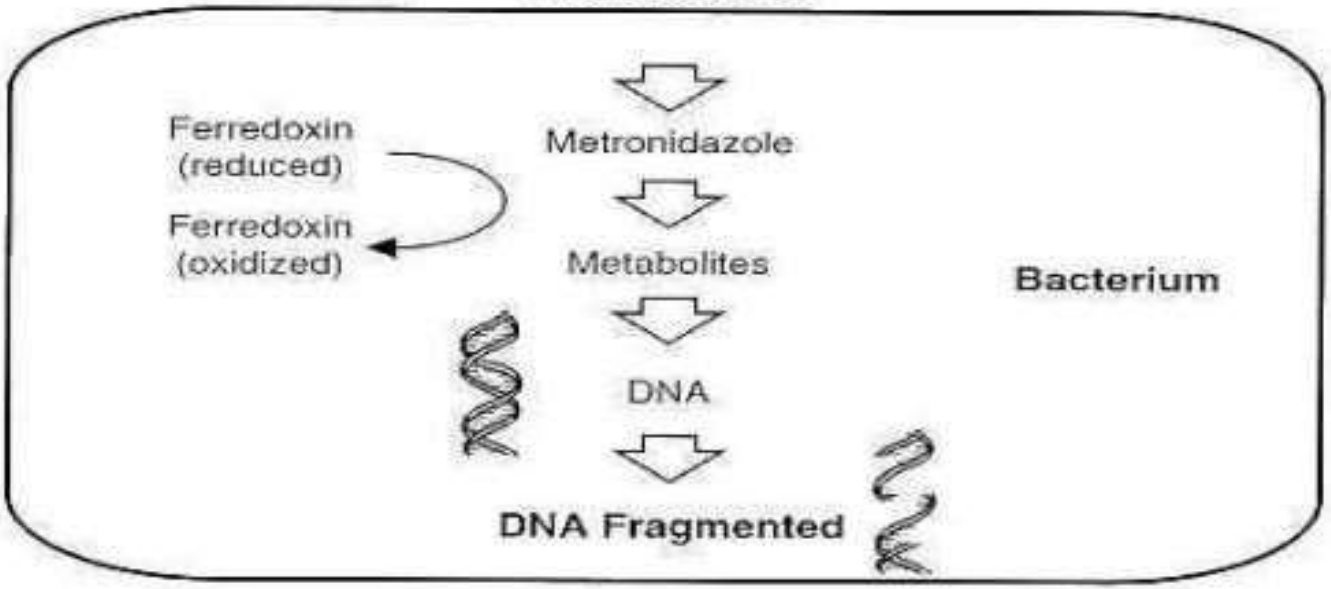
Metabolism of Metronidazole



Mechanism of action of Metronidazole



Metronidazole



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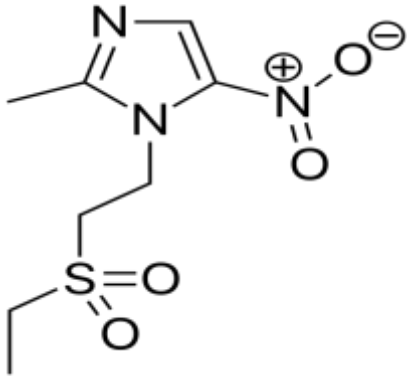
Tinidazole

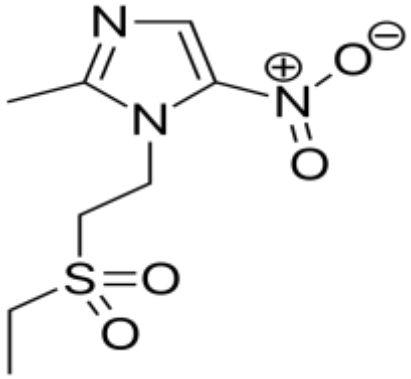


- **Tinidazole** is an anti-parasitic drug used gainst protozoan infections. It is widely known throughout Europe and the developing world as a treatment for a variety of amoebic and parasitic infections. It was developed in 1972 and is a prominent member of he nitroimidazole use of tinidazole for infections from amoebae, giardia, and trichomonas, just like metronidazole.

- Tinidazole may be a therapeutic alternative in the setting of metronidazole tolerance. Tinidazole may also be used to treat a variety of other bacterial infections (e.g., as part of combination therapy for Helicobacter pylori eradication protocols).

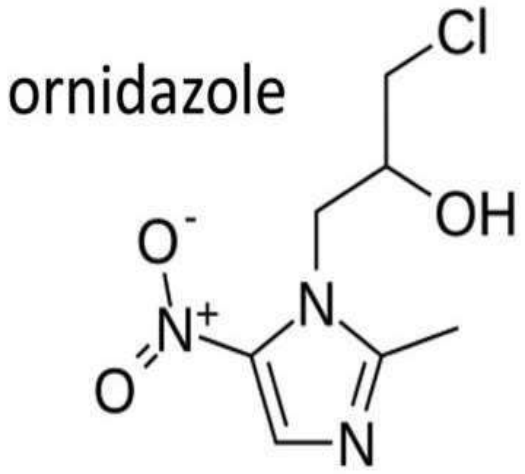
- Elimination half-life is 13.2 ± 1.4 hours. Plasma half-life is 12 to 14 hours
- Drinking alcohol while taking tinidazole causes an unpleasant disulfiram-like reaction, which includes nausea, vomiting, headache, increased blood pressure, flushing, and shortness of breath.

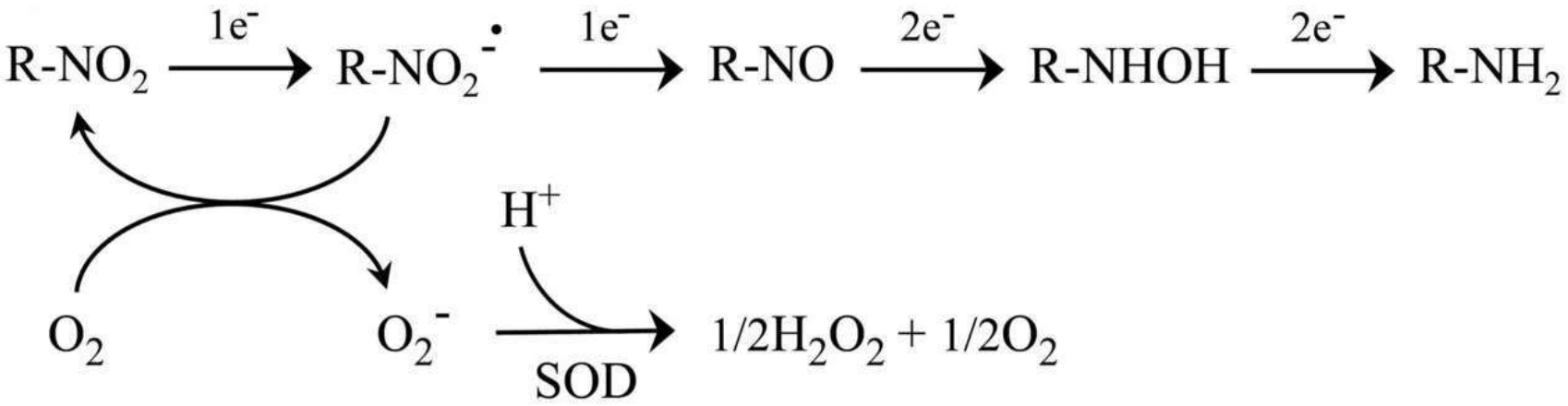
Ornidazole



- **Ornidazole** is a antibiotic used to treat some protozoan infections. It has also been investigated for use in Crohn's disease after bowel resection.
- After passive absorption into bacterium cell, the nitro group of ornidazole is reduced to an amine group by ferrodoxin-type redox systems. The formation of redox intermediate intracellular metabolites is believed to be the key component responsible for killing microorganisms. The drug is active against anaerobic bacteria including *Peptostreptococcus*, *Clostridium*, *Bacteroides fragilis*, *Prevotella*, *Porphyromonas gingivalis*, and *Fusobacterium* as well as protozoa including *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia lamblia*

MOA of Ornidazole





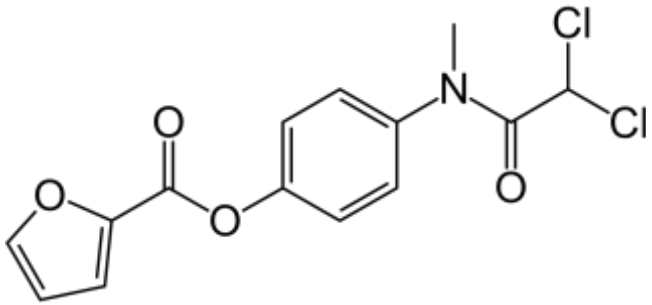
2. Dichloroacetamides: Diloxanide Furoate, Etofamide, Teclozan

Luminal Amebicides

Iodoquinol *Paromomycin *diloxanide furoate

- They have a direct amebicidal effect to the trophozoites and cyst forms.
- Used in: **asymptomatic cyst carriers** and in **intestinal** amebiasis.
- Amebae feed on intestinal Flora so **tetracycline** is added to luminal amebicides to decrease major food source.
- Side effects
- ***iodoquinol*** *include rash, diarrhea, and dose-related peripheral* neuropathy, including a rare optic neuritis.

Diloxanide furoate



- **Diloxanide** is a medication used to treat amoeba infections. It is a second line treatment after paromomycin when no symptoms are present in places where infections are not common. For people who are symptomatic, it is used after treatment with metronidazole or tinidazole. It is taken by mouth.
- Diloxanide generally has mild side effects. Side effects may include flatulence, vomiting, and itchiness. During pregnancy it is recommended that it be taken after the first trimester. It is a luminal amebicide meaning that it only works on infections within the intestines.

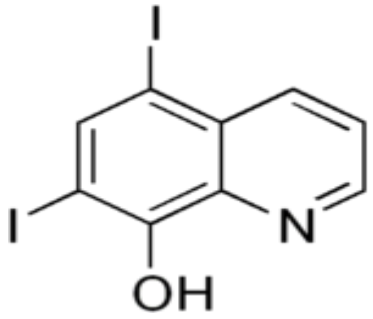
- Dloxanide furoate works only in the digestive tract and is a lumenal amebicide. It is considered second line treatment for infection with amoebas when no symptoms are present but the person is passing cysts, in places where infections are not common. Paromomycin is considered the first line treatment for these cases.
- For people who are symptomatic, it is used after treatment with ambecides that can penetrate tissue, like metronidazole or tinidazole. Diloxanide is considered second-line, while paromomycin is considered first line for this use as well.

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

3. Halogenated 8 Hydroxyquinolines: Clioquinol & Iodoquinol

Iodoquinol

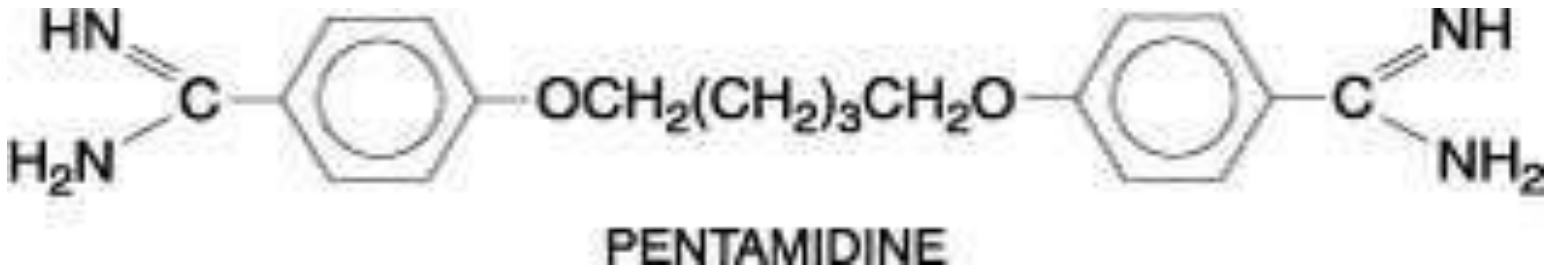


- Iodoquinol is an amebocide used against *Entamoeba histolytica*, and it is active against both cyst and trophozoites that are localized in the lumen of the intestine. It is considered the drug of choice for treating asymptomatic or moderate forms of amebiasis. The mechanism of action is unknown. Iodoquinol is used for diseases caused by moderate intestinal amebiasis.

- Iodoquinol 650 mg tid x 21d

Pentamidine

- Positively charged aromatic diamine
- Accidentally discovered in 1937
- Broad spectrum agent with activity against many protozoa and fungi



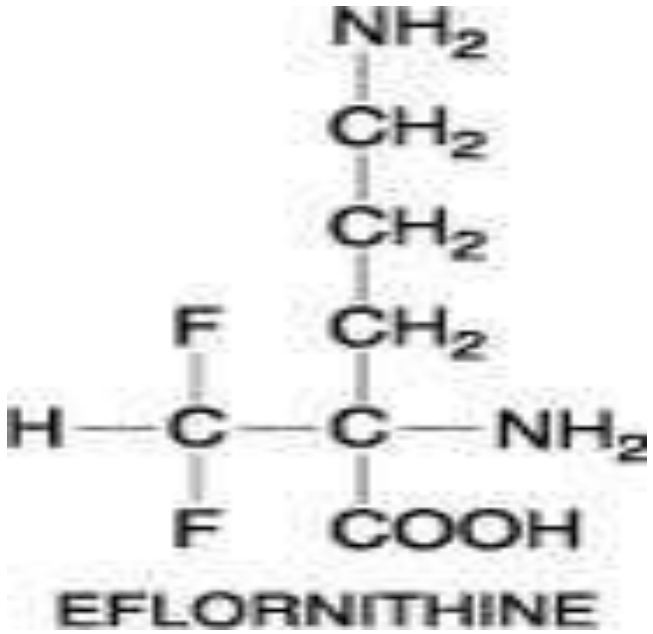
PENTAMIDINE

Mechanism of action

- Exact mechanism not known
- Multiple effects on a single parasite and different mechanisms in different parasites
- Transporter systems (energy dependent high affinity uptake – P_2 purine transporter best characterized)
- Reacts with negatively charged intracellular organelles and leads to;
  - Ribosomal aggregation
  - Inhibition of DNA and protein synthesis
  - Enzyme inhibition
  - Loss of kinetoplast (topoisomerase II inhibition)

Enflornithine

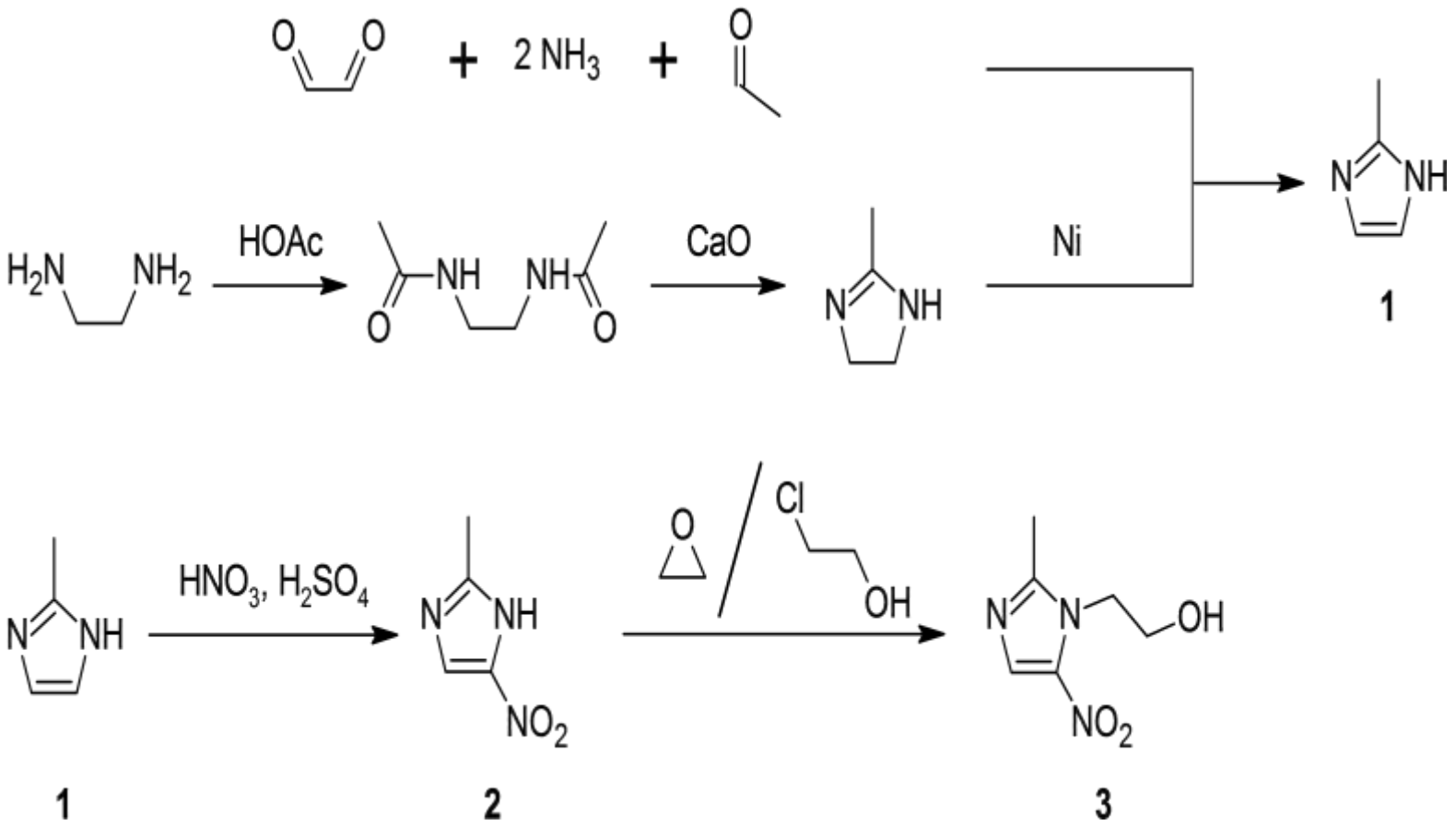
α-D,L difluromethylornithine



Mechanism of action

- Irreversible inhibitor ornithine decarboxylase by covalent binding (rate limiting step in polyamine biosynthesis)
- Polyamines (Putrescine, Spermidine and Spermine) are needed for cell division and normal cell differentiation
- In trypanosomes, spermidine is additionally needed for trypanothione synthesis
- Can also inhibit human enzymes
- T. brucei rhodesiense less sensitive than T. brucei gambiense (effective dose is 10-20 times more)

Synthesis of Metronidazole



THANK YOU.....

SULPHONAMIDES

Description

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

✓ Presence of free amino group

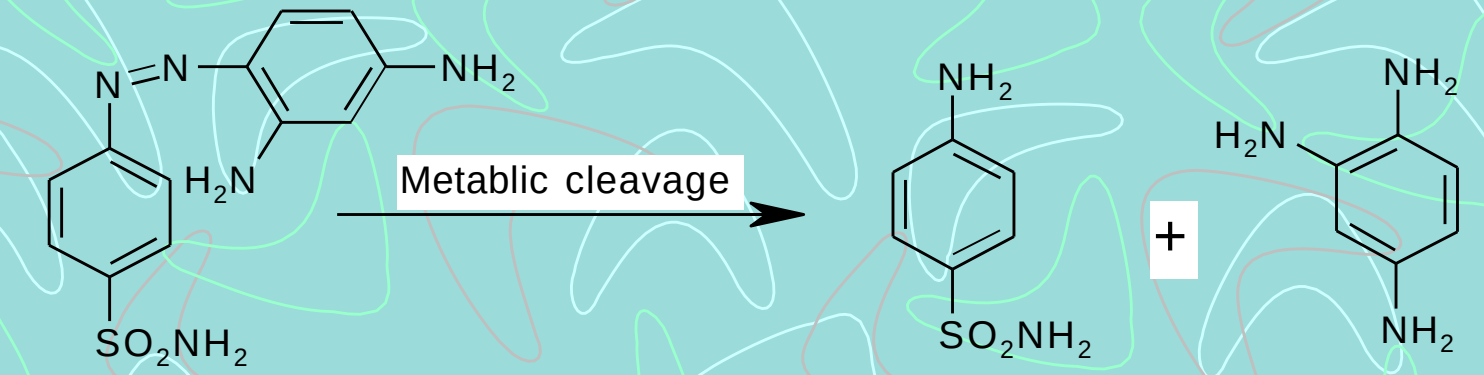
↓

Antibacterial action

✓ Prontosil red → Prodrug

✓ In vitro → Inactive

✓ In vivo → Active

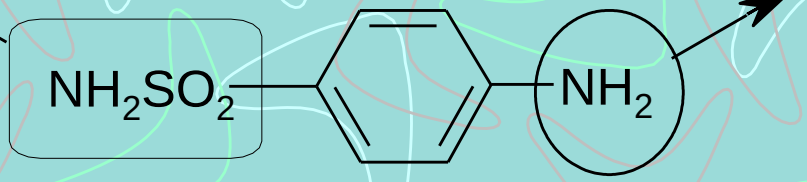


Prontosil Red

Sulphonamide

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

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

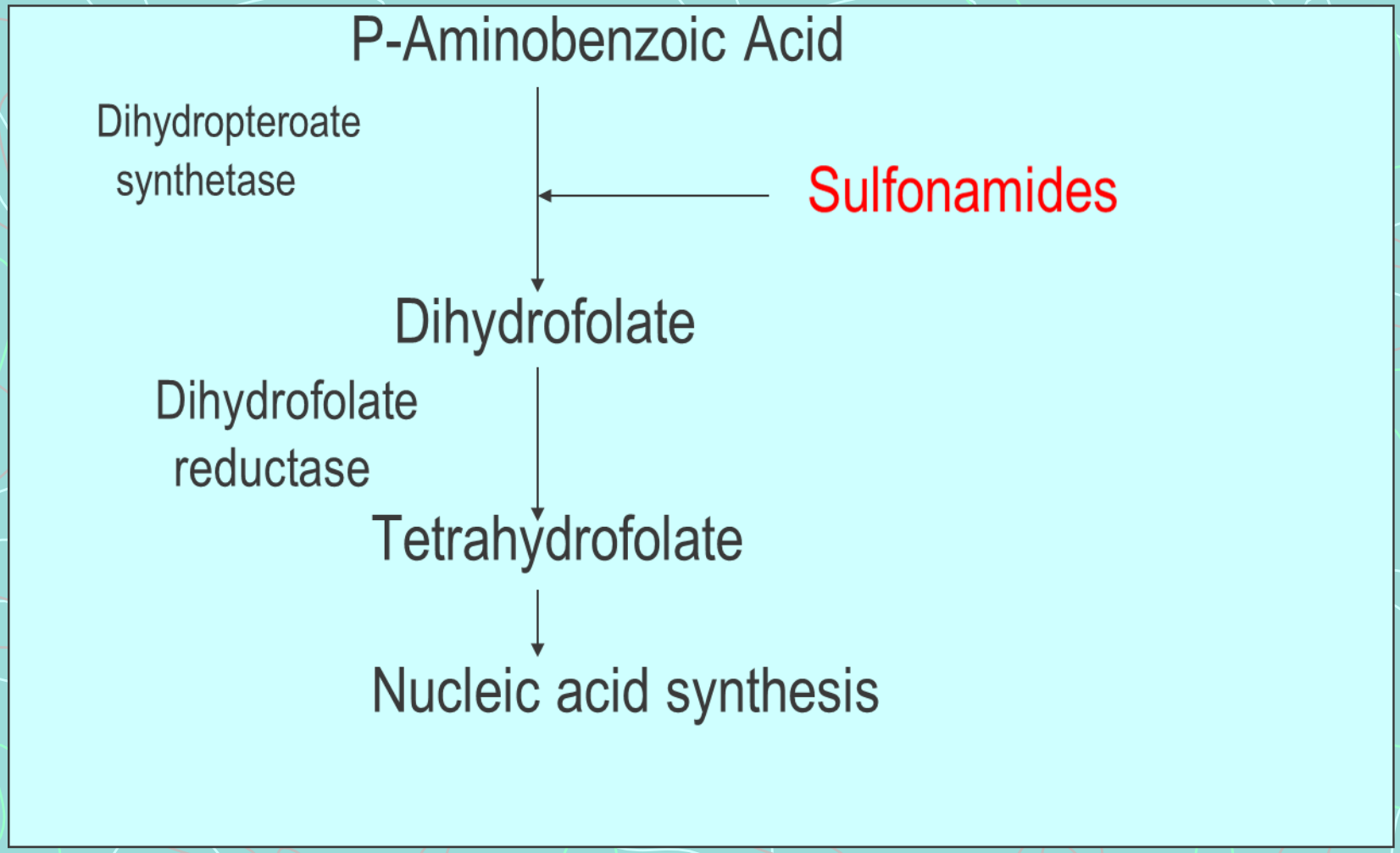


Substitution gives prodrug

Mechanism of action

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

MECHANISM OF ACTION



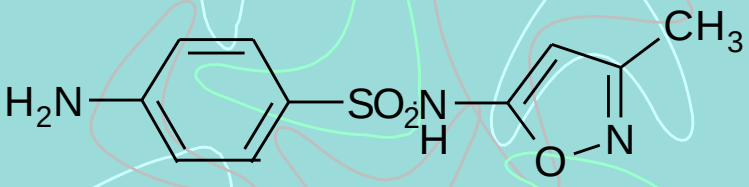
Antibacterial activity

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

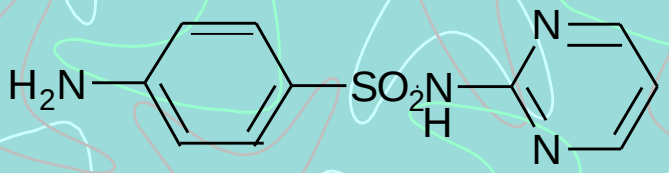
Classification

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

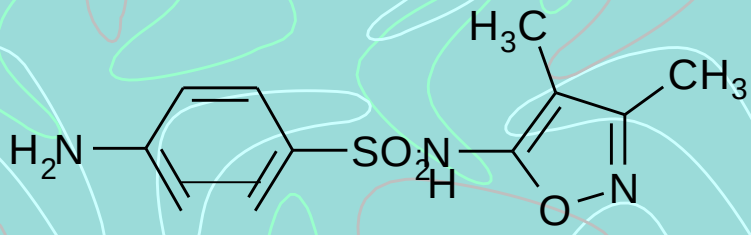
a) Short to intermediate acting sulphonamides.



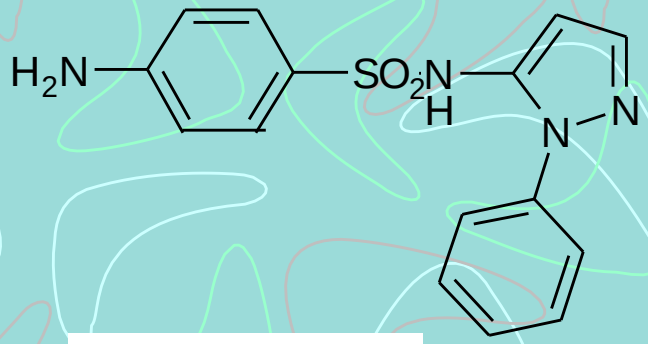
Sulphamethoxazole



Sulphadiazine

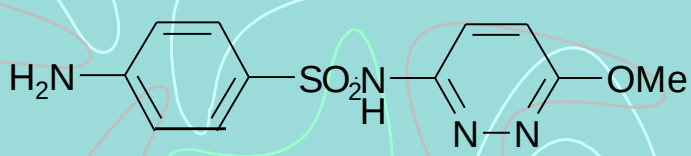


Slpfisoxazole

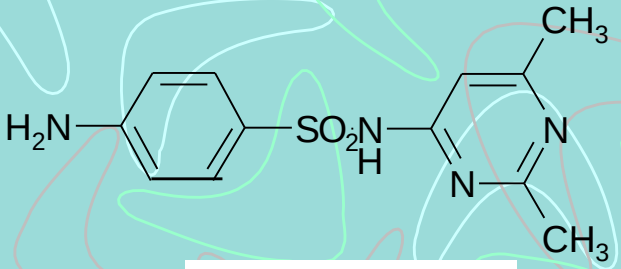


Sulphaphenazole

B. Long acting sulphonamides

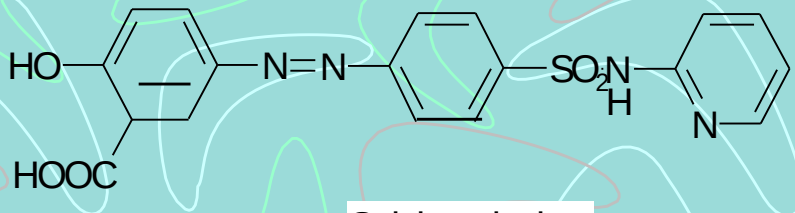


Sulphamethoxypyridazine

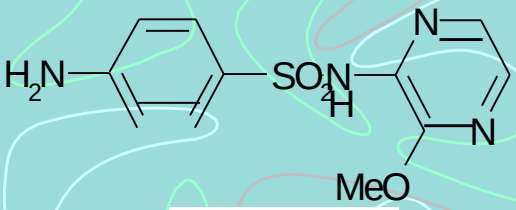


Sulphadimethoxine

C. Extra long acting sulphonamides



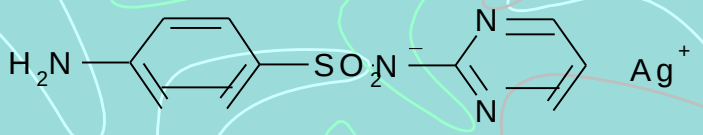
Sulphasalazine



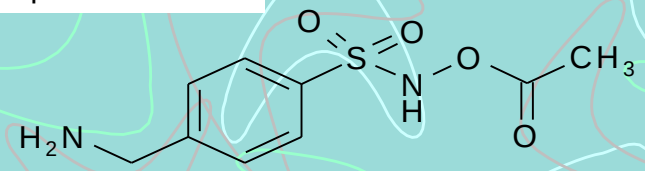
Sulphadiazine

2. Poorly absorbed sulphonamides

Sulphacetamide

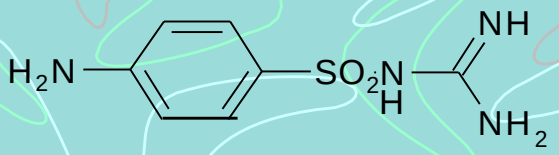


Silver Sulphadiazine

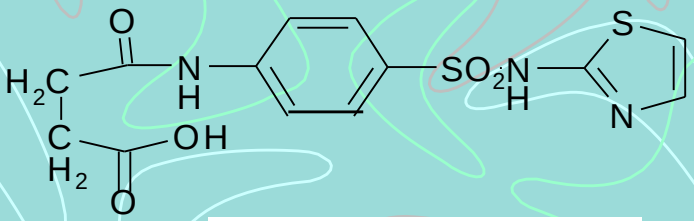


Mafenide acetate

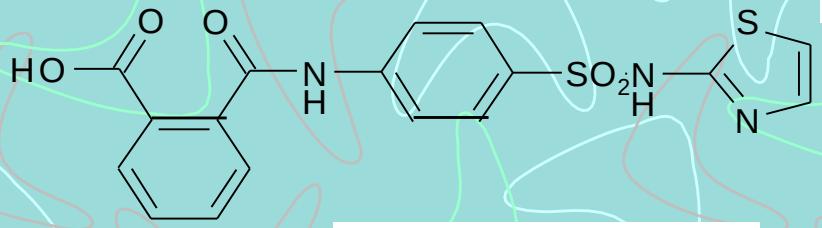
3. Topically used sulphonamides



Sulphaguanidine



Succinyl Sulphathiazole



Phthalyl Sulphathiazole

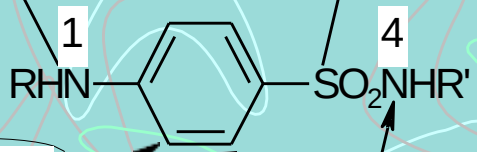
STRUCTURE ACTIVITY RELATIONSHIP

- General

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

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

Sulphur atom should be directly linked to the benzene ring



Substituents at these positions results in devoid of antibacterial activity

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

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

Structure activity relationship of sulphonamide

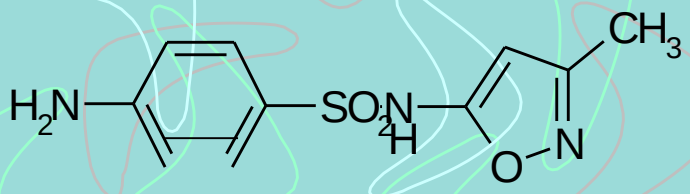
Therapeutic uses

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

Adverse effects

- Hypersensitivity reactions
- Crystalluria,hematuria,renal obstruction.
- Allergic nephritis
- Haemolytic anaemia, aplastic anaemia, thrombocytopenia.
- Kernicterus in new born

Trimethoprim - Sulfamethoxazole combination (Co-trimoxazole)



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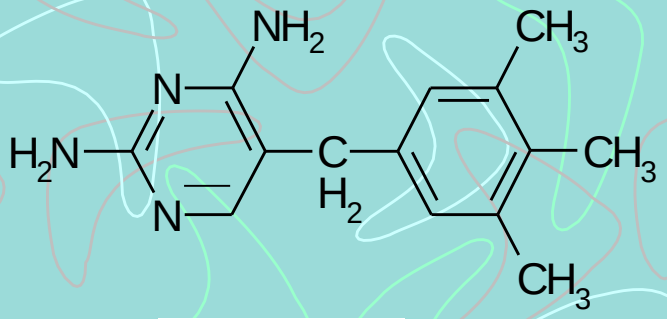
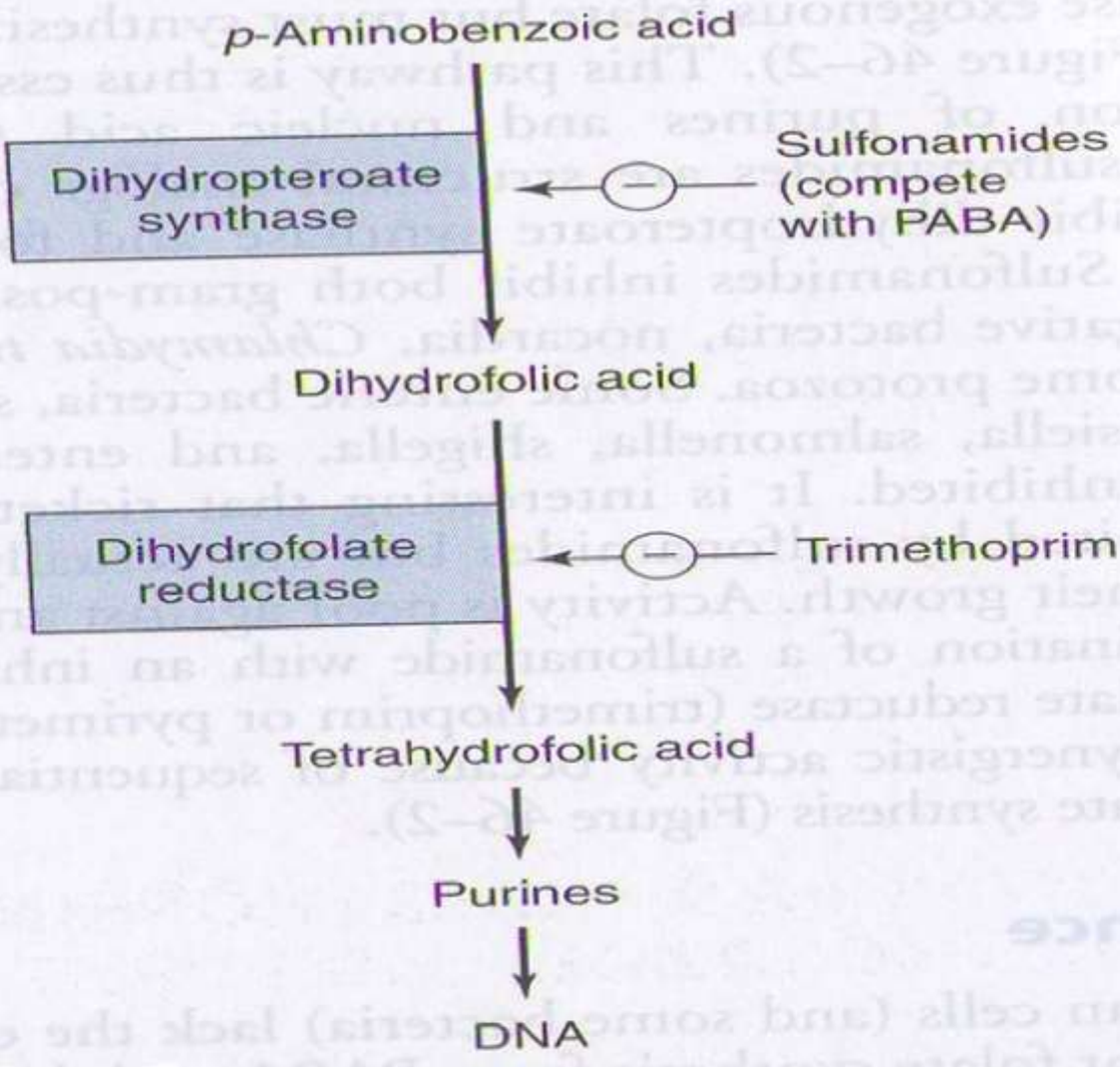


Trimethoprim

Mechanism of action:

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



Actions of sulfonamides and trimethoprim.

Clinical uses

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

Clinical uses continues.....

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

Adverse effects

- Megaloblastic anemia, leukopenia & granulocytopenia (can be prevented by administration of folic acid)
- All side effects associated with sulfonamides

Thank you