

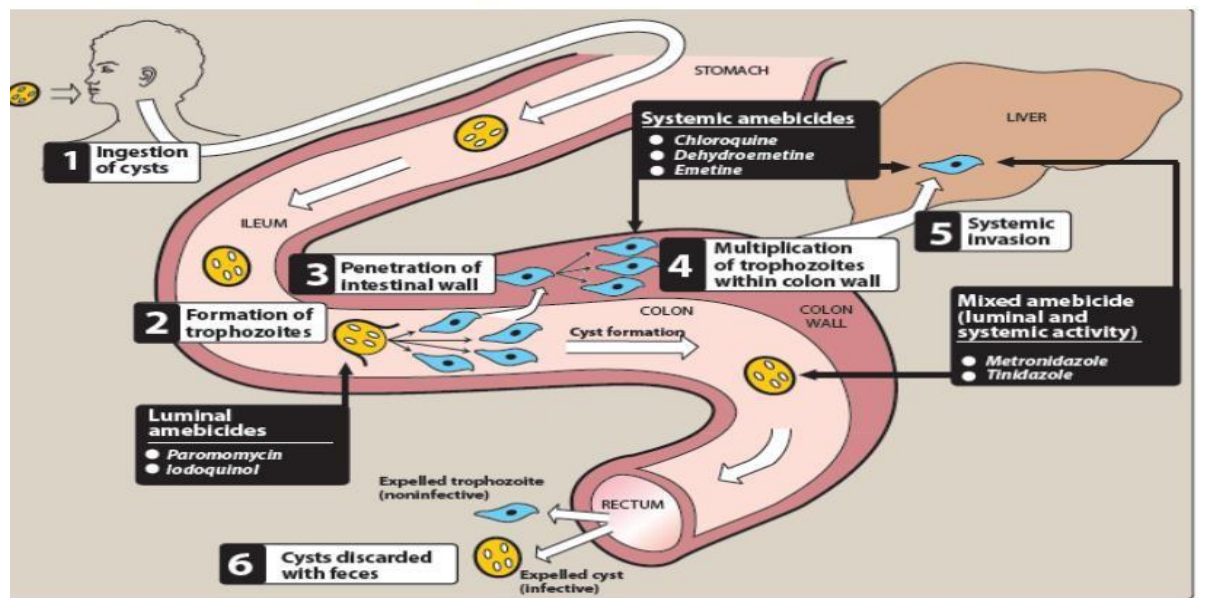
# BALAJI COLLEGE OF PHARMACY



## ANTIPROTOZOAL AGENTS

### Histolytica cysts

Life cycle of *Entameeba histolytica* and the sites of action of amebicidal drugs



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**Definition:**

Antiprotozoal agents are a class of drugs used to treat infections caused by protozoa, which are single-cell organisms, belonging to a group of parasites. Protozoans typically are microscopic and similar to plants and animals as they are eukaryotes, thus having a clearly defined cell nucleus. They are responsible for various diseases in both plants and animals.

**ANTI-PROTOZOAL/AMOEBIC DRUGS**

SN	Pathogens	Diseases
1	<i>Entamoeba histolytica</i>	Amoebiasis
2	<i>Giardia lamblia</i>	Giardiasis
3	<i>Trichomonas vaginalis</i>	Trichomoniasis
4	<i>Trypanosoma brucei</i>	African Sleeping Sickness
5	<i>Trypanosoma cruzi</i>	Chagas disease (American Sleeping Sickness)
6	<i>Leishmania Sps</i>	Leishmaniasis
7	<i>Plasmodium</i>	Malaria
8	<i>Toxoplasma gondii</i>	Toxoplasmosis
9	<i>Cryptosporidium</i>	Cryptosporidiosis

**❖ Amoebiasis:**

- These are drugs useful in infection caused by the anaerobic protozoa *Entamoeba histolytica* and other *Entamoeba* species are generally non-pathogenic.
- Amoebiasis has a worldwide distribution but it is endemic in most parts of India and other developing countries
- Poor environmental sanitation and low socio-economic status are important factors in the spread of the disease, which occurs by fecal contamination of food and water.
- Amoebiasis cause acute dysentery (with blood and mucus in stools) or chronic intestinal amoebiasis (with vague abdominal symptoms, ameboma).
- This parasitic disease is one of the major causes of illness and death in many countries.
- World Health Organization (WHO) has classified this disease as follows:
  1. Asymptomatic
  2. Symptomatic
    - a. Intestinal Amoebiasis
      - i. Dysentery

- ii. Nondysenteric colitis
  - iii. Ameboma
  - iv. Amoebic appendicitis.
- b. Extraintestinal amoebiasis
- i. Liver abscesses
3. Cutaneous involvement of other organs (lungs, brain, spleen).

**Classification of Antiamoebics:**

- a) **Luminal Amoebicides** (Drugs used in intestinal amoebiasis)

Luminal amoebicides act on the lumen of the bowel.

These drugs are particularly used for the treatment of asymptomatic amoebiasis. These are administered at the first stage of infection i.e., upon ingesting cysts. Hence, they prevent the formation of trophozoites and subsequent infection. These drugs are inactive against tissue trophozoites.

EX: Iodoquinol, Pentamidine isethionate, Atovaquone, Diloxanide, Eflornithine

- b) **Systemic Amoebicides** (Drugs used in extraintestinal amoebiasis):

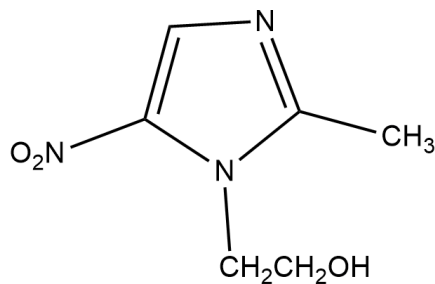
EX: Emetine, Dehydroemetine, Chloroquine.

- c) **Mixed Amoebicides** (Drugs used in both intestinal and extraintestinal amoebiasis)

EX: Metronidazole, Tinidazole, ornidazole.

**Metronidazole:**

It is a 5-nitroimidazole antiprotozoal or Antiamoebics drug, used in the treatment of infections caused by anaerobic Gram-positive and Gram-negative bacteria and protozoa. It is a mixed action amoebicide which exerts antiamoebic actions on systemic as well as luminal trophozoites. It has broad spectrum of activity against Bacteroides, Eubacterium, Clostridium and Peptococcus.

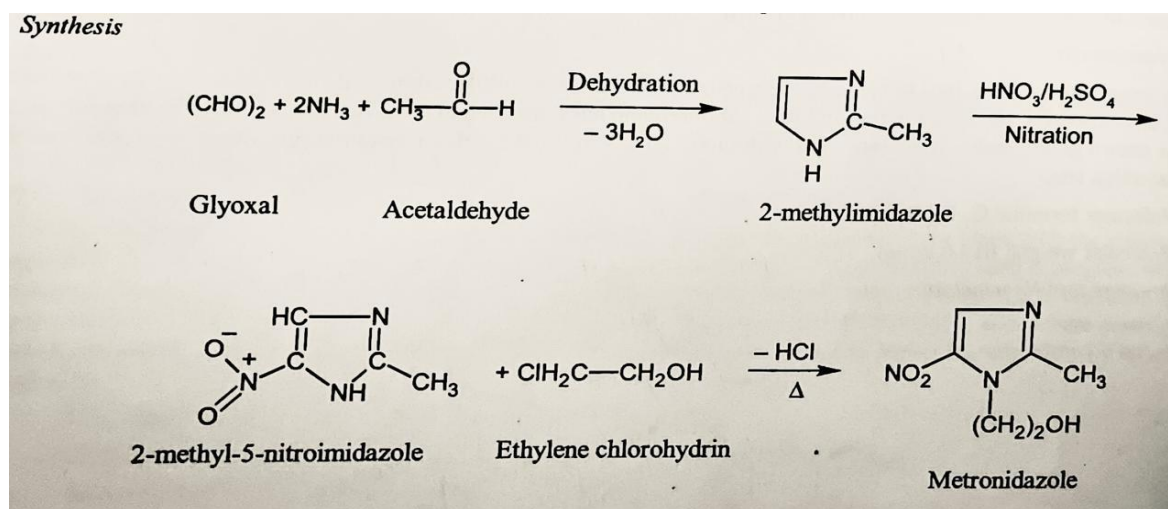


2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol

## MOA:

Metronidazole is selectively toxic to anaerobic and microaerophilic microorganisms. After entering the cell by diffusion, its nitro group is reduced by certain redox proteins operative only in anaerobic microbes to a highly reactive nitro radical which exerts cytotoxicity. Potential reactive intermediates are formed such as nitroxide, nitroso, hydroxylamine, which bind to that of microsomal DNA, Proteins and cell membrane. Reduced metronidazole breaks DNA strand inhibits DNA synthesis and bacterial cell growth.

## Synthesis:

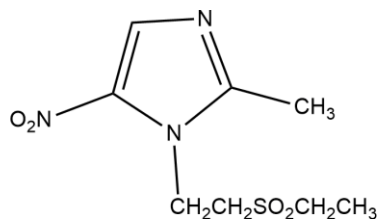


## Therapeutic Uses:

- ❖ It is effective on Amoebiasis, Giardiasis, Trichomonas vaginitis, Anaerobic bacterial infections, Pseudomembranous enterocolitis, Acute necrotizing ulcerative gingivitis, and Helicobacter pylori gastritis/peptic ulcer.

## Tinidazole:

It is an antiparasitic agent and a derivative of 5-nitroimidazole which is effective in the treatment of amoebiasis, giardiasis and trichomoniasis. The toxicity profile of tinidazole is far better than metronidazole.



1-(2-(ethylsulfonyl)ethyl)-2-methyl-5-nitro-1*H*-imidazole

### MOA:

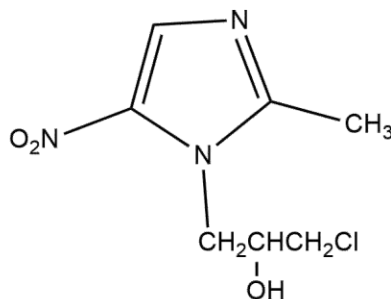
Mechanism of action of tinidazole similar to metronidazole. Nitro group of the tinidazole is reduced by *Trypanosoma vaginalis* to generate a free radical of nitro-anion, which is responsible for the anti-protozoal activity of the drug. The exact mechanism of action of tinidazole against *Giardia* and *Entamoeba* is unknown but it is thought to induce DNA damage and inhibit the synthesis of DNA leading to cytotoxicity.

### Uses:

- ❖ Used in treatment of intestinal amoebiasis (*E. histolytica*), antiprotozoal (i.e., *Trichomonas*, *Giardia*), Antiamoebics and also as an antibacterial agent.

### Ornidazole:

Ornidazole is used in the treatment of protozoal infections and for anaerobic bacterial infections. Chemically, it is a 5-nitroimidazole derivative compounds.



1-chloro-3-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propan-2-ol

### Mechanism of Action:

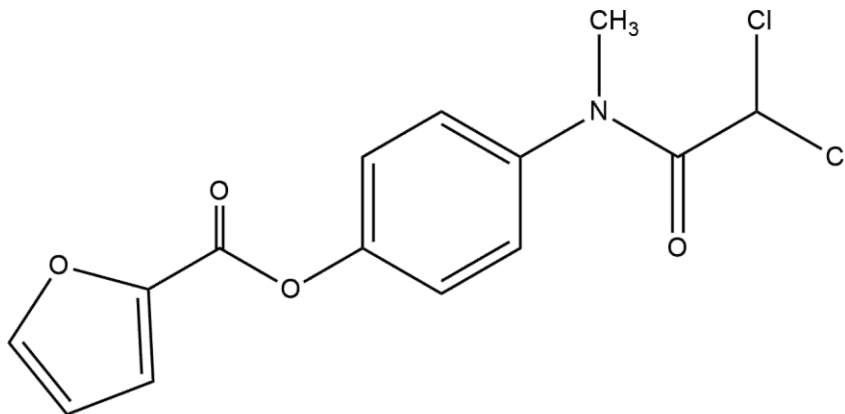
Mechanism of action of ornidazole is similar to Metronidazole.

### Uses:

- ✓ Used in treatment of intestinal amoebiasis (*E. histolytica*), antiprotozoal (i.e., *Trichomonas*, *Giardia*), Antiamoebics and also as an antibacterial agent.
- ✓ It is also used in treatment of stomach, intestine, urinary tract infection.
- ✓ It is also used in treatment of Crohn's disease.

**Diloxanide:**

It is an antiprotozoal drug effective against *Entamoeba histolytica* and some other protozoal infections. Chemically, it is an aromatic ester of diloxanide and 2-furoic acid.



4-(2,2-dichloro-*N*-methylacetamido)phenyl furan-2-carboxylate

**Mechanism of Action:**

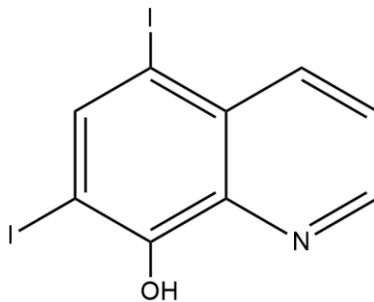
Diloxanide is a potent luminal amoebicide but is not active against tissue trophozoites. The exact mechanism of action of diloxanide is not known. However, it is known to kill trophozoites that produce cysts.

**Uses:**

- ❖ Used in treatment of amoeba infection
- ❖ Also used in treatment of asymptomatic intestinal amoebiasis caused by *E. histolytica*.

**Iodoquinol**

Iodoquinol belongs to the class of 8-hydroxyquinolines. It is cidal towards the cyst forming amoebic trophozoites.



5,7-diiodoquinolin-8-ol

**MOA:**

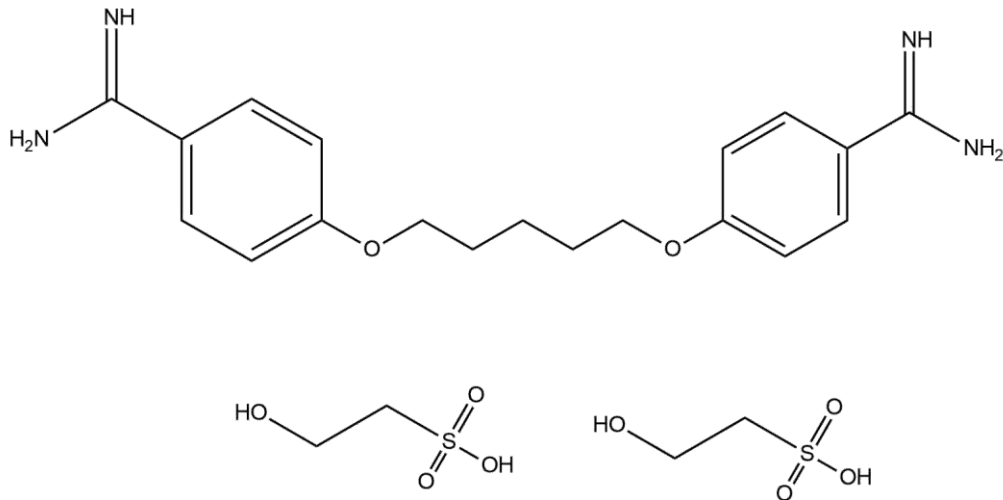
Destroys the trophozoites of *E. histolytica*.

Uses:

- Used in treatment of amoeba infection
- Also used in treatment of asymptomatic intestinal amoebiasis caused by *E. histolytica*.

### Pentamidine Isethionate

Pentamidine isethionate is a diamidine derivative. It is more potent but more toxic than pentavalent antimony compounds (E.g: Sodium stibogluconate). It is usually reserved for cases resistant to chemotherapy in treatment of Kala-azar. It is also quite active against *Trypanosoma* spp, *pneumocystis carinii* etc.



4,4'-(pentane-1,5-diylbis(oxy))dibenzimidamide bis(2-hydroxyethanesulfonate)

### Mechanism of Action

The exact mechanism of action of the drug is not known. It binds to protozoal DNA and inhibits DNA replication and function.

### Therapeutic Uses

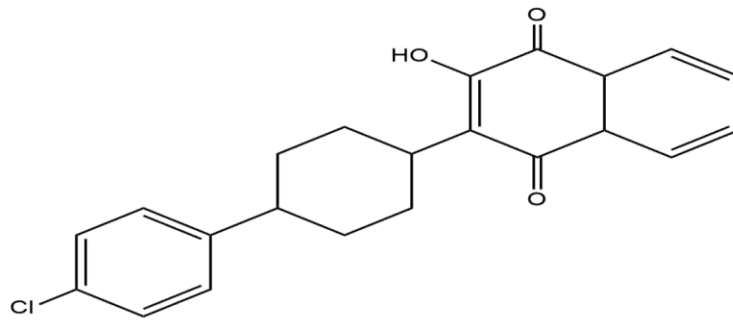
1. It is used in the treatment of visceral leishmaniasis and mucocutaneous leishmaniasis resistant to pentavalent antimony therapy.
2. It is used in the treatment of *Pneumocystis jiroveci* pneumonia.
3. It is also used as an alternative to suramin in the treatment of trypanosomiasis.

### Atovaquone

Atovaquone is a synthetic naphthaquinone. It is commonly used as anti-malarial drug and acts as erythrocytic schizonticide as well as active against preerythrocytic stage of *P.falciparum* and other plasmodia. It is also active against *Pneumocystis jiroveci* and *Toxoplasma gondii*.

### MOA:

It inhibits pyrimidine synthesis and further preventing DNA synthesis and also blocks the mitochondrial electron transport at complex III of the respiratory chain of protozoa.



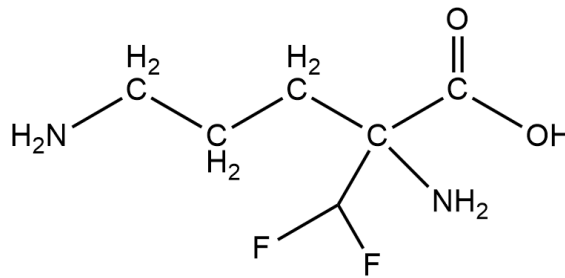
2-(4-(4-chlorophenyl)cyclohexyl)-3-hydroxynaphthalene-1,4(4aH,8aH)-dione

### Uses:

- It is used in the treatment of bacterial, viral, or fungal pneumonias and mycobacterial disease, and malaria and also used in pneumocystis pneumonia.

### Eflornithine:

Eflornithine is a difluoromethylated ornithine compound. It is used to treat African trypanosomiasis (sleeping sickness) and excessive hair growth on the face in women (facial hirsutism).



2,5-diamino-2-(difluoromethyl)pentanoic acid

### Mechanism of Action:

The drug causes irreversible inhibition of ornithine decarboxylase and thus inhibits the biosynthesis of protozoal polyamines. The polyamines are required for cell division and differentiation in protozoa.

### Therapeutic Uses:

1. It is used in the treatment of West African trypanosomiasis caused by *T.brucei*, *T.gambiense* and has good accumulation in CSF, making it useful in advanced CNS disease conditions of African trypanosomiasis.
2. It is also useful in reducing the rate of growth of facial hair in women.