Anti-protozoal agents

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Antiprotozoal agents

- In the United States and other countries of the temperate zone, protozoal diseases are of minor importance
- Protozoal diseases are highly prevalent in tropical Third World countries, where they infect both human and animal populations
- Cause suffering, death, and enormous economic hardship
- Protozoal diseases that are found in the United States are malaria, amebiasis, giardiasis, trichomoniasis, toxoplasmosis, and, as a direct consequence of the AIDS epidemic, *P. carinii* pneumonia (PCP)

Antiprotozoal agents

- Amebiasis- *Entamoeba histolytica*
- Can invade the wall of the colon or other parts of the body (e.g., liver, lungs, skin)
- Other protozoal species that colonize the intestinal tract and cause enteritis and diarrhea are *Balantidium coli* and the flagellates, *G. lamblia* and *Cryptosporidium* spp
- Trichomoniasis, a venereal disease caused by the flagellated protozoan *T. vaginalis*
- *P. carinii* is an opportunistic pathogen that may colonize the lungs of humans and other animals and, under the right conditions, can cause pneumonia
- *Toxoplasma gondii* is an obligate intracellular protozoan that is best known for causing blindness in neonates

Antiprotozoal agents

- Various forms of trypanosomiasis, chronic tropical diseases caused by pathogenic members of the family Trypanosomidae, occur both in humans and in livestock
- African sleeping sickness caused by *Trypanosoma gambiense* (West African), *Trypanosoma rhodesiense* (East African), or *Trypanosoma congolense*; and
- South American sleeping sickness (Chagas disease) caused by *Trypanosoma cruzi*
- Chagas disease is the most serious and generally the most resistant to chemotherapy
- Leishmaniasis is a chronic tropical disease caused by various flagellate protozoa of the genus *Leishmania*
- More common visceral form caused by *Leishmania donovani*, called *kala-azar*, is similar to Chagas disease

Antiprotozoal agents

Drug treatment of amebiasis, giardiasis, trichomoniasis

- Diloxanide furoate
- Metronidazole
- Nitazoxanide
- Tinidazole

Treatment of pneumocystis

- Atovaquone
- Pentamidine isethionate
- Sulfamethoxazole–trimethoprim
- Trimetrexate glucuronate

Treatment of trypanosomiasis

- *Benznidazole*
- Eflornithine
- Melarsoprol
- Nifurtimox
- Pentamidine isethionate
- Suramin sodium

Treatment of leishmaniasis

- *Sodium stibogluconate*
- Miltefosine

Antimalarials

- Artemisinins (arteether, artemether, artesunate, dihydroartemisinin)
- Atovaquone–proguanil
- Chloroquine
- Halofantrine
- Lumefantrine
- Mefloquine
- Pyrimethamine
- Quinine

Anthelmintics

- Albendazole
- Diethylcarbamazine
- Ivermectin
- Mebendazole
- Oxamniquine
- Praziquantel
- Pyrantel pamoate
- Thiabendazole

Scabicides and pediculocides

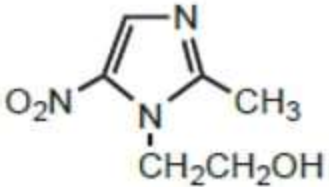
- Crotamiton
- Lindane
- Permethrin
- Pyrethrin
- Spinosad

Metronidazole

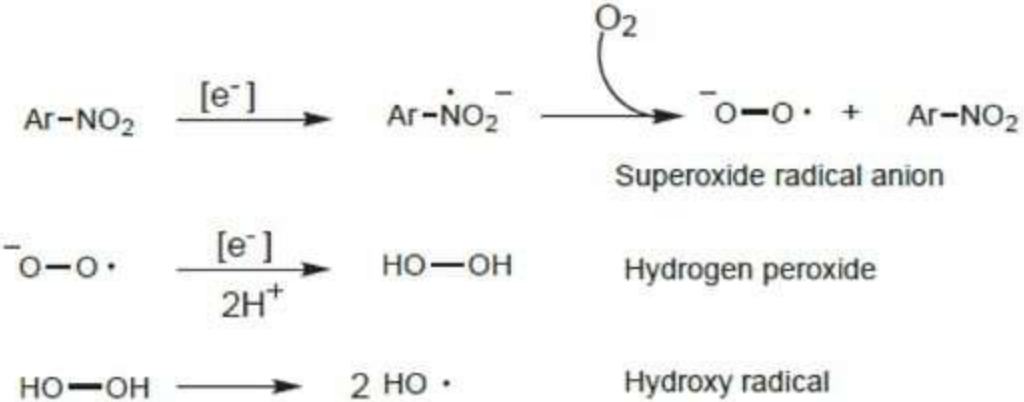
- Most useful of a group of antiprotozoal nitroimidazole derivatives that have been synthesized in various laboratories throughout the world
- First marketed for the topical treatment of *T. vaginalis* for vaginitis
- Also possesses useful amebicidal activity and is, in fact, effective against both intestinal and hepatic amebiasis
- Other protozoal diseases as giardiasis and balantidiasis
- It is particularly active against Gram-negative anaerobes, such as *Bacteroides* and *Fusobacterium* spp
- It is also effective against Gram-positive anaerobic bacilli (e.g., *Clostridium* spp.) and cocci (e.g., *Peptococcus*, *Peptidostreptococcus* spp.).

Metronidazole

- Because of its bactericidal action, metronidazole has become an important agent for the treatment of serious infections (e.g., septicemia, pneumonia, peritonitis, pelvic infections, abscesses, meningitis) caused by anaerobic bacteria
- Mechanism- reactive intermediate formed in the microbial reduction of the 5-nitro group of metronidazole covalently binds to the DNA of the microorganism, triggering the lethal effect
- Potential reactive intermediates include the nitroxide, nitroso
- hydroxylamine, and amine
- Ability of metronidazole to act as a radiosensitizing agent
- is also related to its reduction potential



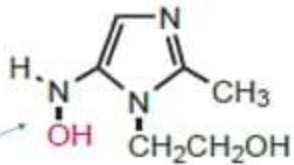
Mechanism of metronidazole



Formation of ROS from nitroaryl compounds.

Metronidazole

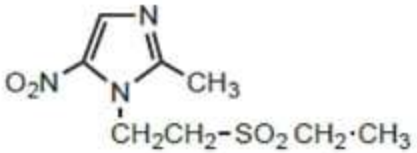
- Pale yellow crystalline substance that is sparingly soluble in water
- It is stable in air but is light sensitive
- 2-hydroxy metabolite is active; other metabolites are inactive



- Solutions of metronidazole hydrochloride are unsuitable for intravenous administration because of their extreme acidity
- Must be reconstituted with sterile water to yield 5 mL of a solution having a concentration of 100 mg/mL and a pH ranging from 0.5 to 2.0
- Resulting solution must then be diluted with either 100 mL of normal saline or 5% dextrose and neutralized with 5 mEq of sodium bicarbonate to provide a final solution of metronidazole base with an approximate concentration of 5 mg/mL and a pH of 6 to 7

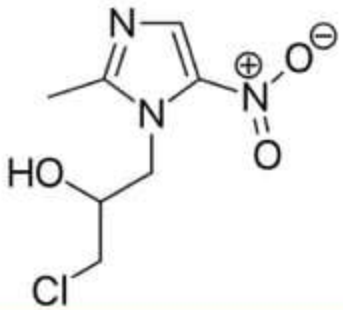
Tinidazole

- Approved by the U.S. Food and Drug Administration (FDA) for the treatment of amebiasis, giardiasis, and trichomoniasis
- Also to be highly effective against *Helicobacter pylori* infections
- Drug is rapidly and completely absorbed following oral administration and can be administered with food to reduce GI disturbance
- Mechanism of action- similar to metronidazole
- Tinidazole appears to mimic the actions of metronidazole
- Also effective against some protozoa that are resistant to metronidazole



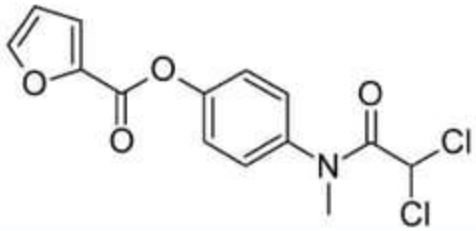
Ornidazole

- Antibiotic used to treat protozoan infections
- Antimicrobial spectrum is similar to that of metronidazole
- It was first introduced for treating trichomoniasis before being recognized for its broad anti-protozoan and anti-anaerobic-bacterial capacities



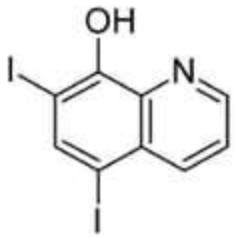
Diloxanide

- 2-furoate ester of 2,2-dichloro-4-hydroxy-*N*-methylacetanilide
- It was developed as a result of the discovery that various ,α-α-dichloroacetamides possessed amebicidal activity in vitro
- Used in the treatment of asymptomatic carriers of *E. histolytica*
- White crystalline powder and is administered orally only as 500-mg tablets



Iodoquinol

- Diiodohydroxyquin is a yellowish to tan microcrystalline, light-sensitive substance that is insoluble in water
- It is recommended for acute and chronic intestinal amebiasis but is not effective in extraintestinal disease
- Because a relatively high incidence of peripheral neuropathy has occurred with its use, iodoquinol should not be used routinely for traveler's diarrhea



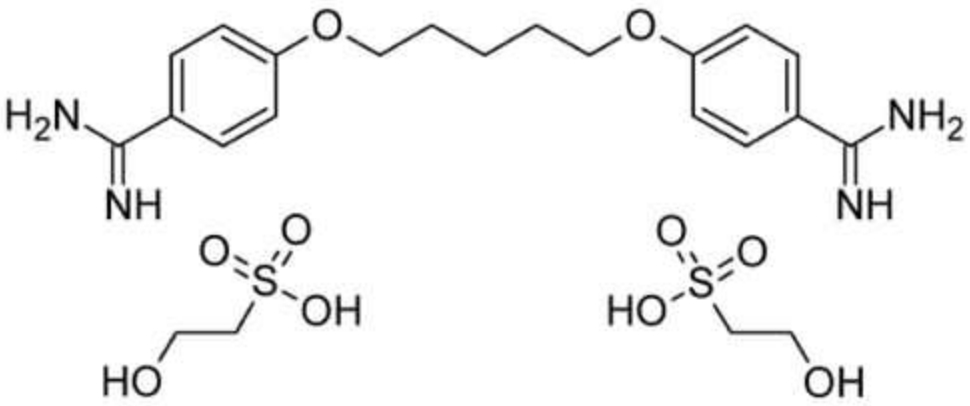
Pentamidine Isethionate

- Water-soluble crystalline salt that is stable to light and air
- Principal use of pentamidine is for the treatment of pneumonia caused by the opportunistic pathogenic protozoan *P. carinii*, a frequent secondary invader associated with AIDS
- Drug may be administered by slow intravenous infusion or by deep intramuscular injection for PCP or in an aerosol form
- Both the inhalant (aerosol) and parenteral dosage forms of pentamidine isethionate are sterile lyophilized powders
- Must be made up as sterile aqueous solutions prior to use by sterile water for injection

Pentamidine Isethionate

- Common adverse reactions- cough and bronchospasm (inhalation) and hypertension and hypoglycemia (injection)
- Used for the prophylaxis and treatment of African trypanosomiasis. It also has some value for treating visceral leishmaniasis
- Prophylaxis- treatment given or action taken to prevent disease
- Because, Pentamidine rapidly disappears from the plasma after intravenous injection and is distributed to the tissues, where it is stored for a long period

Pentamidine Isethionate

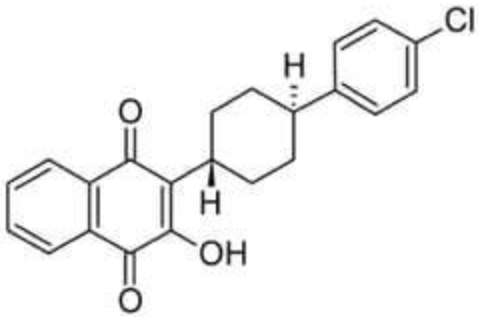


Atovaquone

- Highly lipophilic, water-insoluble analog of ubiquinone 6, an essential component of the mitochondrial electron transport chain in microorganisms
- Structural similarity between atovaquone and ubiquinone suggests that thereby interfere with the function of electron transport enzymes
- Originally developed as an antimalarial drug, but *Plasmodium falciparum* was found to develop a rapid tolerance to its action
- Recommended alternative to trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment and prophylaxis of PCP in patients intolerant to this combination
- High fat content, increases atovaquone absorption

Atovaquone

- It is extensively protein bound (99.9%)
- Half-life of the drug ranges from 62 to 80 hours
- Primary side effect is gastrointestinal intolerance

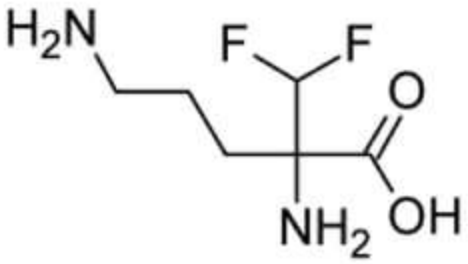


Eflornithine

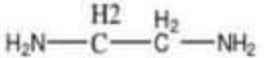
- Used for the treatment of West African sleeping sickness, caused by *Trypanosoma brucei gambiense*
- It is specifically indicated for the meningoencephalitic stage of the disease
- Eflornithine is a myelosuppressive drug that causes high incidences of anemia, leukopenia, and thrombocytopenia
- Complete blood cell counts must be monitored during the course of therapy
- Supplied as the hydrochloride salt
- It may be administered either intravenously or orally
- Approximately 80% of the unchanged drug is excreted in the urine

Eflornithine

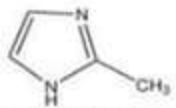
- Mechanism- irreversible inactivation of ornithine decarboxylase by eflornithine is accompanied by decarboxylation and release of fluoride ion
- Enzyme is involved in the synthesis polyamines which are regulators of growth processes



Metronidazole- Synthesis

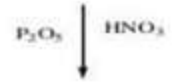


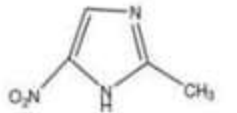
ethane-1,2-diamine



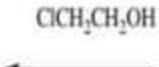
2-methyl-1*H*-imidazole

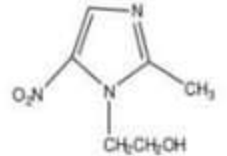
Synthesis of Metronidazole





2-methyl-5-nitro-1*H*-imidazole





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