Anti-Parasitic Agents:
Anti-Protozoal Agents

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CHAPTER 32

Drugs Used to Treat Parasitic Infections

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Drugs covered in this chapter:

TREATMENT OF AMEBIASIS, GIARDIASIS, AND TRICHOMONIASIS:
- Metronidazole
- Nitazoxanide
- Tinidazole

TREATMENT OF PNEUMOCYSTIS:
- Atovaquone
- Penamidine isethionate
- Sulfamethoxazole-trimethoprim

TREATMENT OF TRYPANOSOMIASIS:
- Benznidazole
- Eflornithine
- Melarsoprol
- Niturtimox
- Pentamidine isethionate
- Suramin sodium

TREATMENT OF LEISHMANIASIS:
- Sodium stibogluconate
- Miltefosine

TREATMENT OF MALARIA:
- Artemisinins (artemether, artesunate, dihydroartemisinin)
- Atovaquone-proguanil
- Chloroquine
- Lumefantrine
- Mefloquine
- Piperaquine, primaquine, quinine
- Tafenoquine

TREATMENT OF HELMINTH INFECTIONS:
- Albendazole
- Ivermectin
- Mebendazole
- Moxidectin
- Praziquantel
- Pyrantel pamoate

TREATMENT OF SCABIES AND PEDICULOSIS:
- Benzyl alcohol
- Crotamiton
- Lindane
- Permethrin
- Spinosad

Protozoal Diseases

- Amebiasis
- Giardiasis
- Trichomoniasis
- Pneumocystis Carinii Pneumonia (PCP)
- Trypanosomiasis
- Leishmaniasis
- Malaria: given individual file
- Toxoplasmosis
- Helminthic infections: given individual file
- Scabies & pediculosis

Protozoal Diseases

Table 32.1 Diseases Associated With Protozoal Infections and Their Characteristics

Disease	Organism	Life Stages	Infected Organ/Cells	Transmitter
Amebiasis	*Entamoeba histolytica*	Cyst/trophozoite	Intestine/liver	Contaminated food/ water
Giardiasis	*Giardia lamblia*	Cyst/trophozoite	Intestine/liver	Contaminated water
Trichomoniasis	*Trichomonas vaginalis*	Trophozoite	Vagina/urethra/prostate	Sexual contact
Pneumocyctis pneumonia (PCP)	*Pnemocystis jirovecii*	Yeastlike	Lung	Airborne
Trypanosomiasis				
Sleeping Sickness	*Trypanosoma brucei*	Trypomasbigotes	CNS	Tsetse fly
Chagas Disease	*Trypanosoma cruzi*	Trypomasbigotes/ amastigote	Heart	Reduviid bug
Leishmaniasis	*Leishmania spp*	Promastigote/amastigote	Skin/systemic	Female sandflies
Malaria	*Plasmodium spp*	Sporozoite/merozoite/ trophozoite/gametes	Liver/red blood cells	*Anopheles* mosquito

ORGANISMS THAT COMMONLY CAUSE VAGINITIS

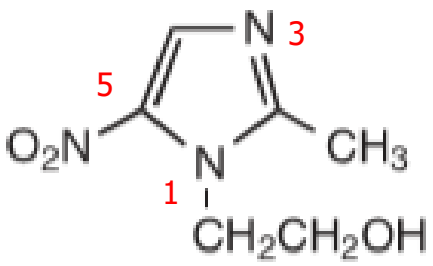
Vaginitis also can be caused by *Haemophilus vaginalis* (bacteria) or *Candida albicans* (fungus), which are treated differently from the protozoal infection.

Chemical Classifications for Antiprotozoal Agents

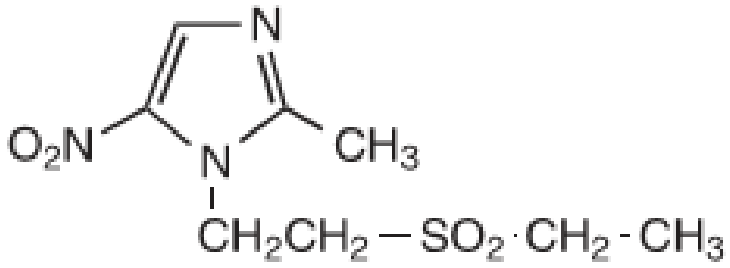
- Nitro-aryl:
- ✓ nitro-imidazole: metronidazole, tinidazole
- ✓ nitro-thiazole: nitazoxanide
- ✓ nitro-furan: nitrofurantoin, …
- Bis-amidine: pentamidine
- Naphthoquinone: atovaquone
- Naphthyl-urea: suramin
- Ornithine analogue (diamino/amino acid analogue): eflornithine
- Quinoline: iodoquinol
- Arsenic, antimony compounds: melarseprol, stibogluconate
- Azo-pyridine: phenazopyridine
- Arsenic, antimony compounds
- Benzyl alcohol, benzyl benzoate
- Benzamide: crotamiton
- Cyclohexan: lindane
- Pyrethroid derivatives: permethrin

Nitro-Imidazoles as Anti-Protozoals

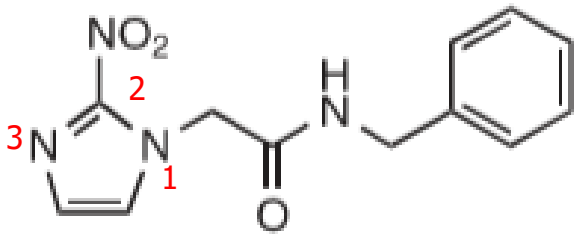
- Compare structures to introduce SAR:



Metronidazole

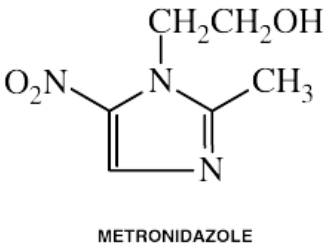


Tinidazole



Benznidazole

Nitro-imidazole: Metronidazole



METRONIDAZOLE

- Chemistry: imidazole-N1-ethanol
- ✓ IUPAC name: 2-methyl 5-nitro-…
- MOA: destructive effect on critical cell components: DNA, Pr, …
- ✓ as a prodrug(PDG):reactive metabolites: reactive oxygen species(ROS)
- Metabolites: biologically active ones:
- ✓ hydroxylamine (-NHOH) derivative
- ✓ nitro radical anion derivative
- ✓ Hydroxy-Methyl (HM) derivative
- ✓ acetic acid derivative
- Dosage forms: oral tablet; topical; rectal; vaginal suppository; injection
- No PB

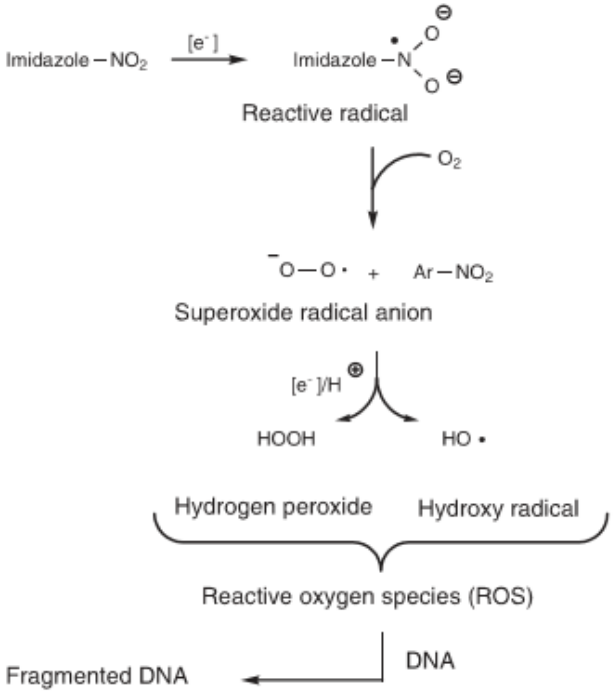
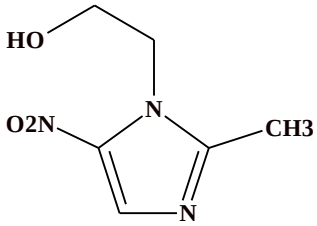


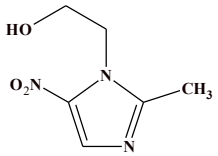
Figure 32.3 Formation of reactive oxygen species (ROS) from nitroimidazole compounds.

Metabolism of Metronidazole



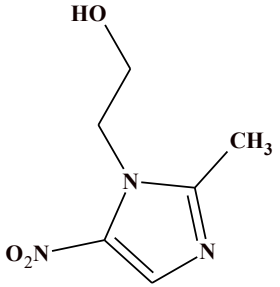
- Biologically in/active metabolites:

✓ hydroxylamine: active metabolite



✓ nitro radical anion: active metabolite

✓ Hydroxy-Methyl (HM): active metabolite



✓ acetic acid derivative : active metabolite

✓ acetamide & oxalate derivatives : in-active metabolite

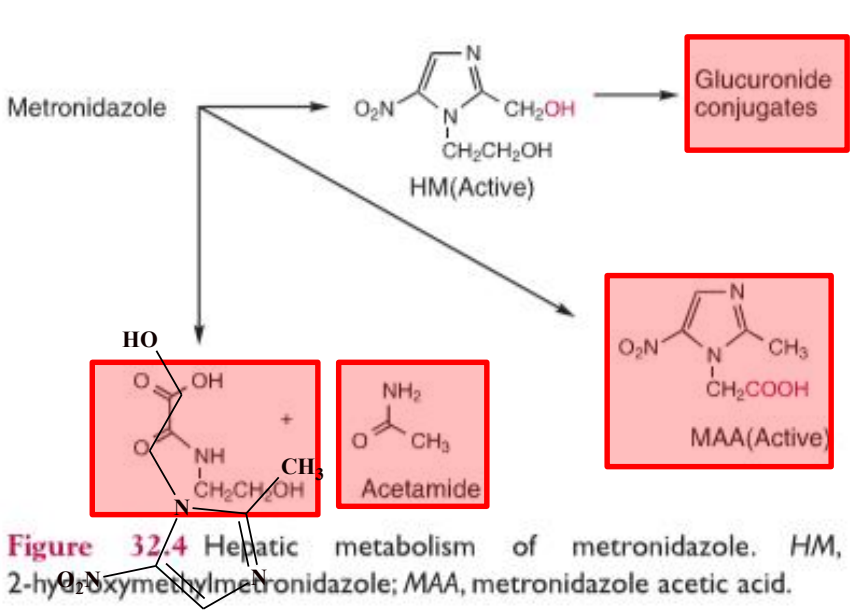


Figure 32.4 Hepatic metabolism of metronidazole. *HM*, 2-hydroxymethylmetronidazole; *MAA*, metronidazole acetic acid.

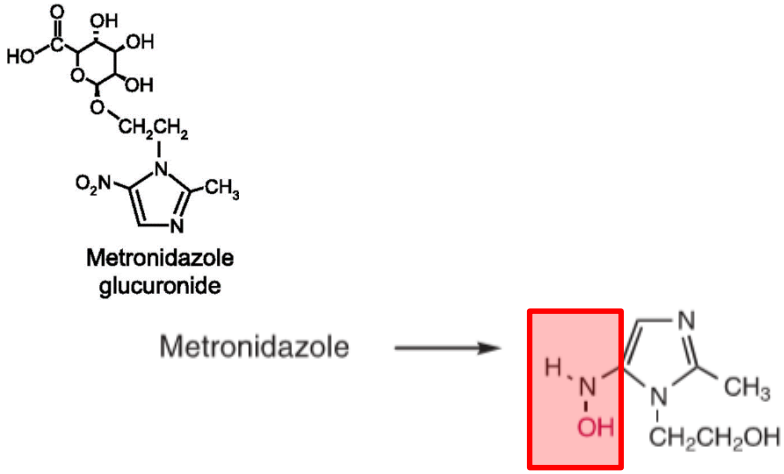
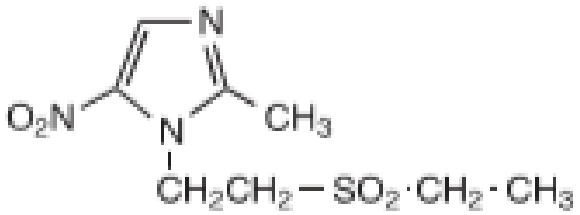


Figure 32.2 Anaerobic metabolic activation of metronidazole.

Nitro-Imidazole: Tinidazole

- Chemistry: 5-nitro- imidazole-N1-…
- Mimics metronidazole

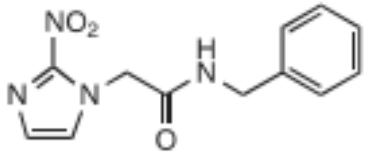


Tinidazole

- MOA:

- Also against some metronidazole resistant protozoa

Nitro-Imidazoles: Benznidazole



Benznidazole

- Chemistry: 2-nitro-imidazole
- MOA: may partially catalyze formation of ROS through nitro-reductase
  - ✓ metabolic activation via protozoal prostaglandin $F_{2\text{-alpha}}$ synthase:
  - ✓ leading to formation of glyoxal: DNA & genetic damage
- Therapeutic application:
  - ✓ against circulating form of *Trypanosome cruzi*

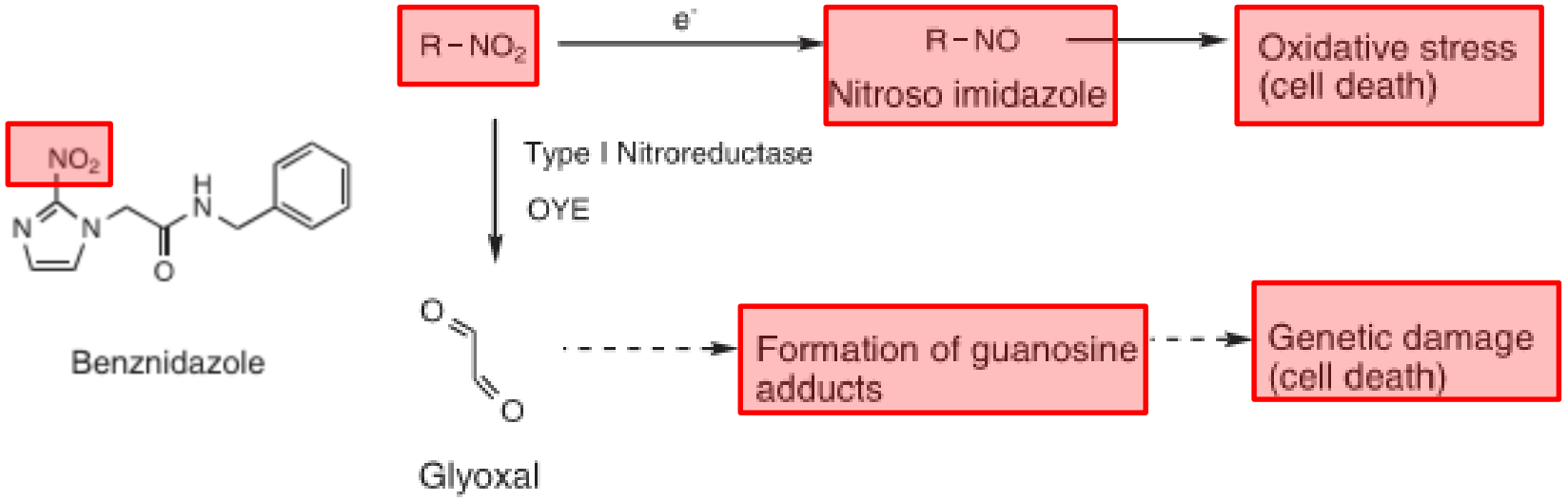
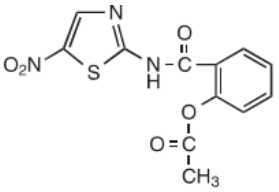


Figure 32.7 Proposed mechanism of action of benznidazole. *OYE*, old yellow enzyme (a prostaglandin $F_{2\alpha}$ synthase).

Nitro-Thiazole: Nitazoxanide (NTZ)



Nitazoxanide

- Nitro-thiazole: higher redox potential
- MOA: pyruvate-ferredoxin oxidoreductase (PFOR) inhibitor
  - ✓ disruption of protozoal bioenergetics
- Metabolites:
  - ✓ hydroxylamine: active metabolite
  - ✓ de-acetylated nitazoxanide: active metabolite
- Therapeutic application:
  - ✓ first as orphan
  - ✓ diarrhea caused by *Giardia lambelia*
  - ✓ trichomoniasis
  - ✓ Helicobacter Pylori
  - ✓ various helminths

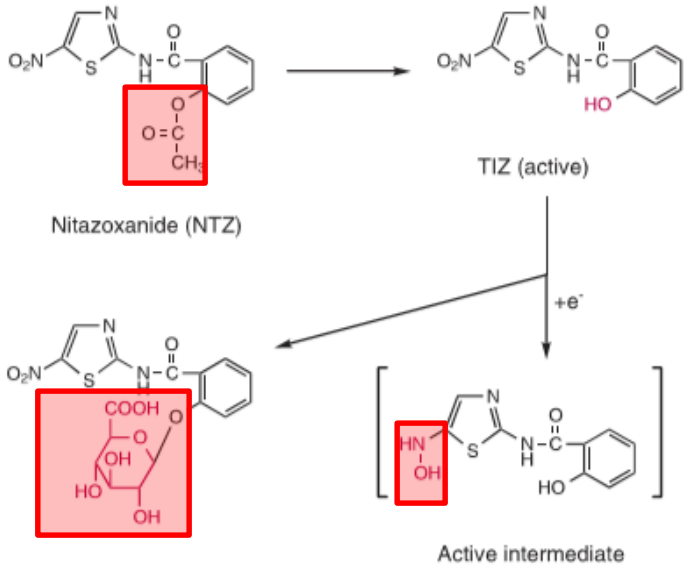
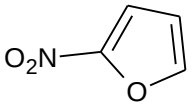


Figure 32.5 Metabolic activation of nitazoxanide. *TIZ*, tizoxanide.

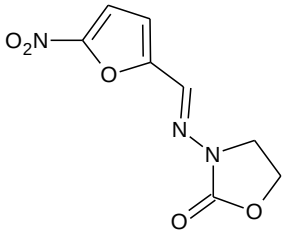
Nitro-Furans as Anti-Protozoals



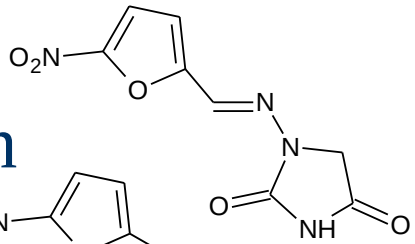
- Compare substitutes in nitro-furans:

✓ nitrofurazone

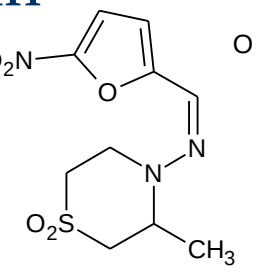
✓ furazolidone

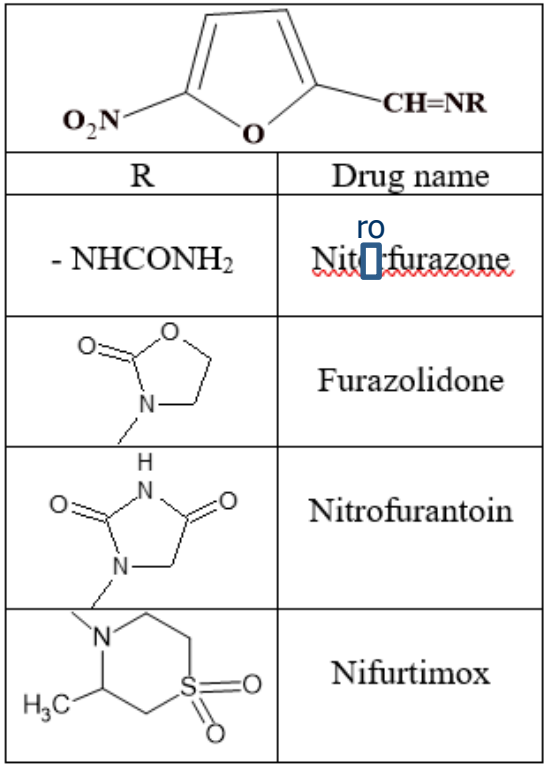


✓ nitrofurantoin



✓ Nifurtimox





- MOA: mostly nitro reduction related

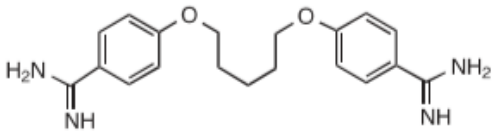
Drugs Against Pneumocystis Pneumonia (P…P): Pneumocystis Carinii Pneumonia (PCP) & Pneumocystis jirovecii Pneumonia (PJP)

- Co-trimoxazole (sulfamethoxazole & trimethoprim):
- ✓ SMX-TMP

- Pentamidine

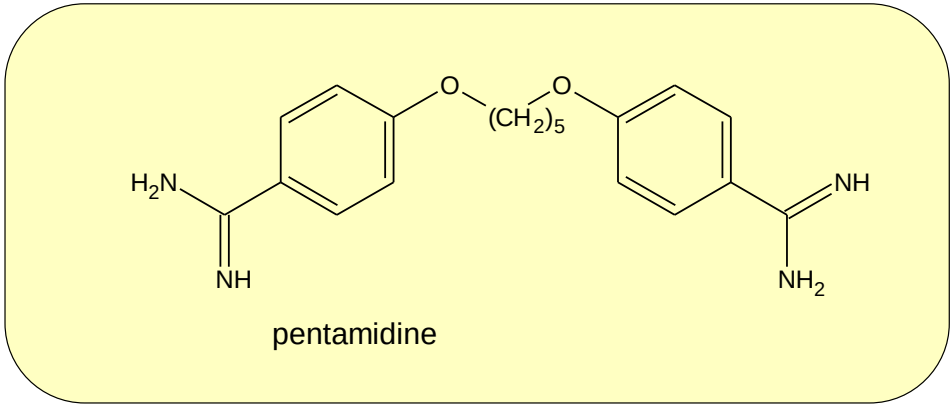
- Atovaquone

Bis-amidine: Pentamidine



Pentamidine isethionate

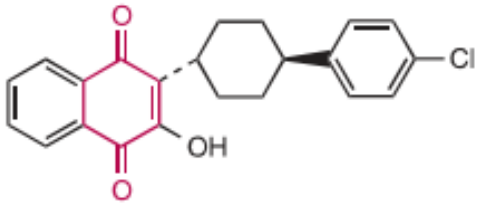
- Chemistry:
- ✓ as isethionate ($HO\text{-}CH_2CH_2\text{-}SO_3H$) salt
- MOA: DNA cleavage & DNA topoisomerase inhibitor
- ✓ hydrogen bond of amidine to AT rich
- ✓ N3 of adenine; 4-5 base pairs
- ✓ DNA inter-strand cross bonding through binding to second adenine
- ✓ might work different in various protozoa
- Not cross BBB
- Therapeutic application:
- ✓ as prophylaxis/second line in PCP
- ✓ trypanosomiasis
- ✓ leishmaniasis
- Dosage forms: injection (IV); aerosol



pentamidine

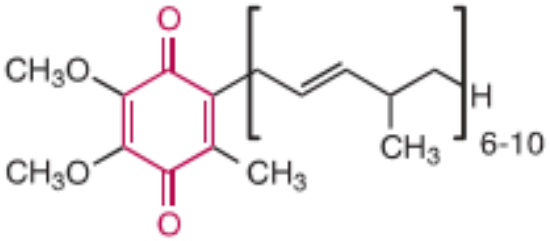
Naphthoquinone: Atovaquone

- Chemistry: naphthoquinone
- ✓ UBQ6-analog: UBQ reductase inhibitor
- ✓ stereospecific: trans > cis
- ✓ lipophil: recommended with fat meal
- MOA: inhibit mitochondrial respiratory chain



Atovaquone

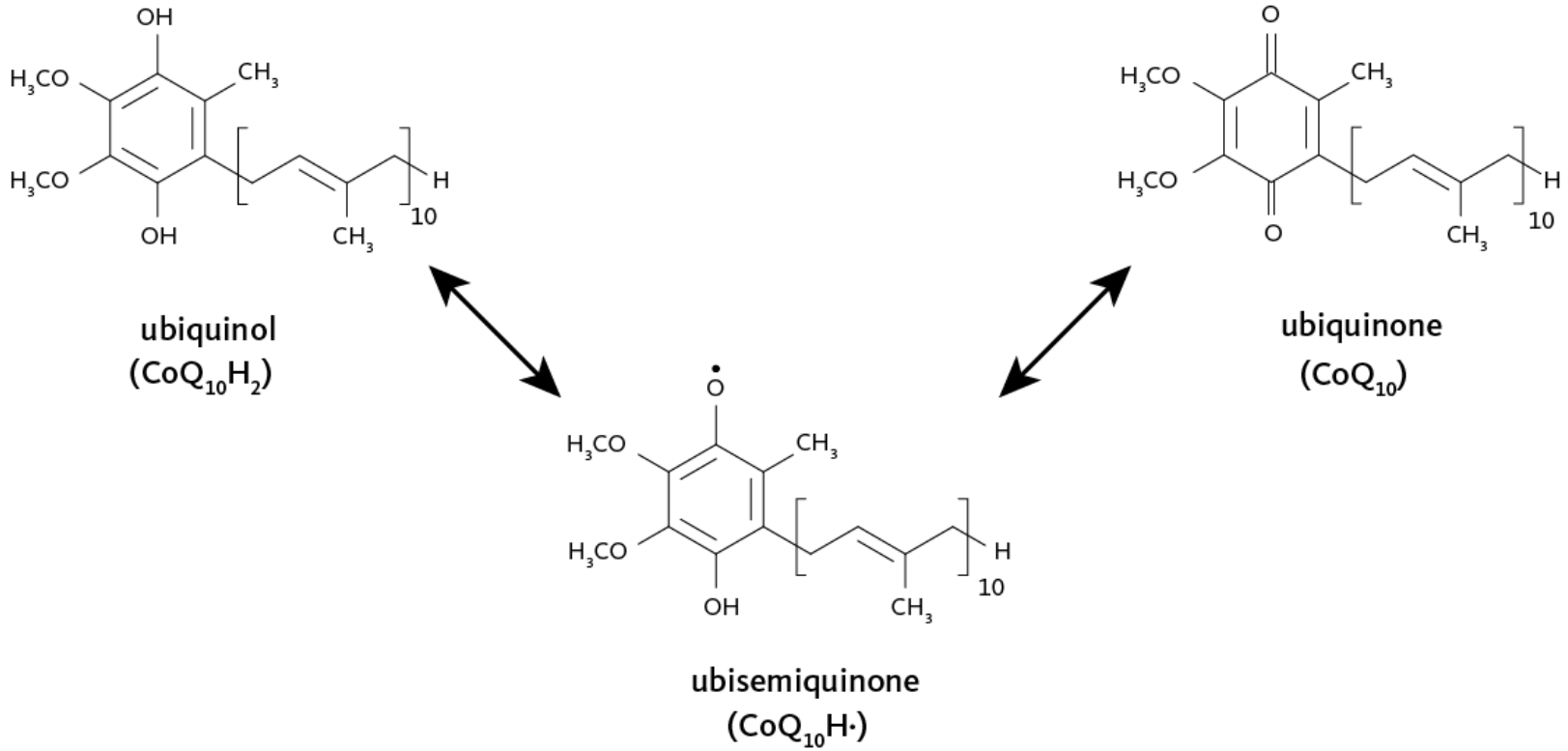
- Therapeutic application:
- ✓ first as anti-malarial
- ✓ in PCP (PJP)
- ✓ alternative to co-trimoxazole (SMX-TMP)
- ✓ in toxoplasmosis



Ubiquinone

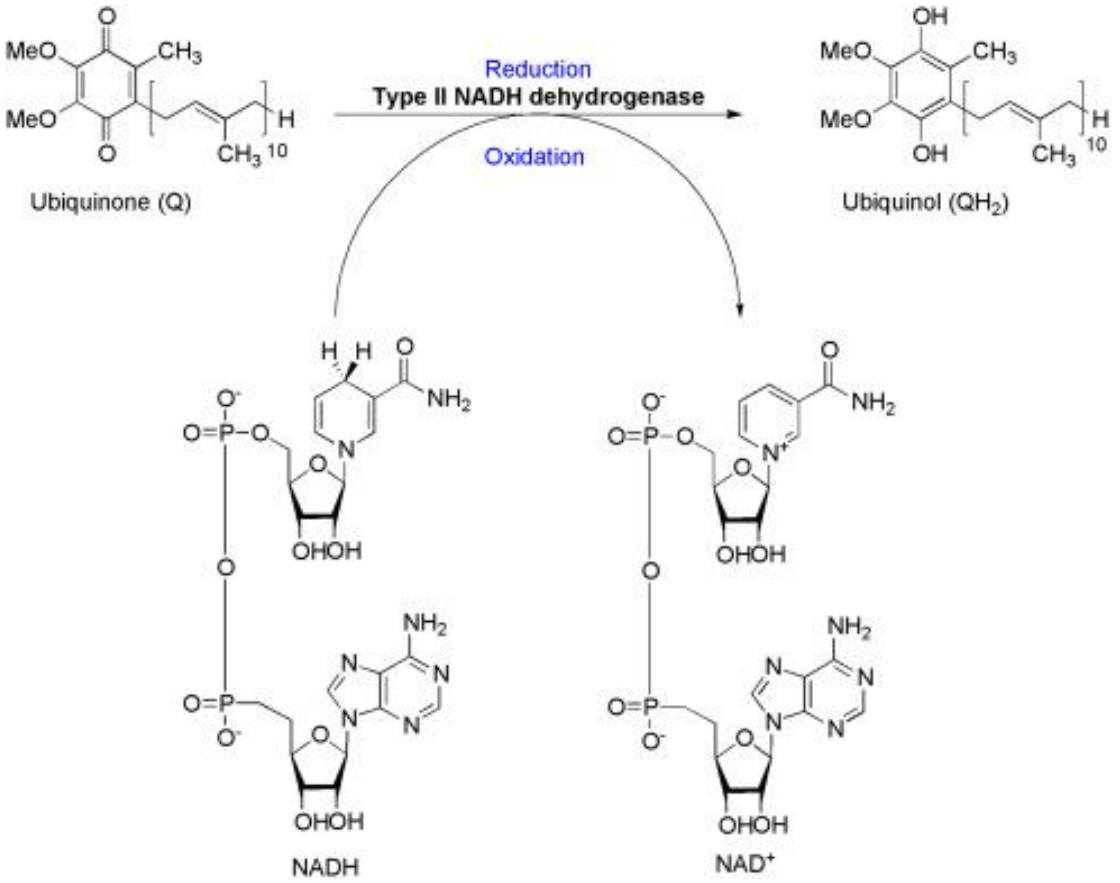
Ubiquinone as CoQ_{10} & Reduced Forms ($CoQ_{10}H$ & $CoQ_{10}H_2$)

Figure 1. The Different Redox Forms of Coenzyme Q_{10}



Coenzyme Q_{10} exists in three oxidation states: the fully reduced ubiquinol form ($CoQ_{10}H_2$), the radical semiquinone intermediate ($CoQ_{10}H\cdot$), and the fully oxidized ubiquinone form (CoQ_{10}).

UBQ Reductase Using NADH-NAD as Cofactor



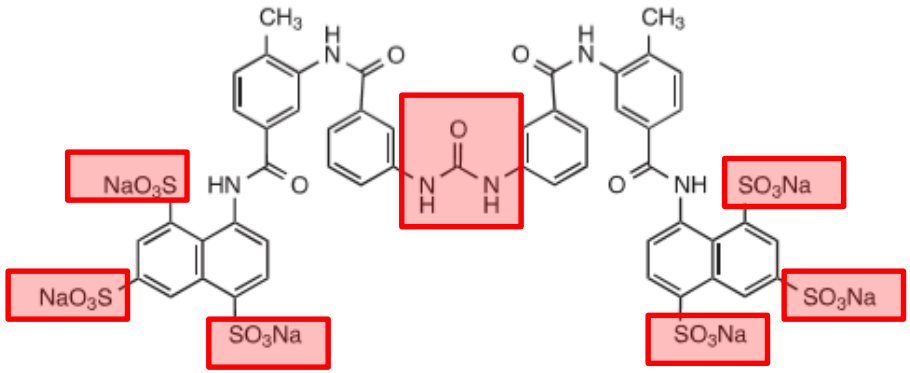
Drugs Against Trypanosmiasis

- Suramine: sodium salt
- Eflornithine
- Pentamidine
- Nifurtimox
- Benznidazole

Naphthyl-urea: Suramin Sodium

- Chemistry: bis-naphthyl-urea: bis-hexa-sulfonated
- ✓ water soluble: highly ionic: not cross BBB
- MOA: affinity to binding to critical enzymes:
- ✓ dehydrogenase & kinase & DHFR & Thymdine kinase & glycolytic enzymes
- ✓ blocks energy source by inhibiting glycolysis

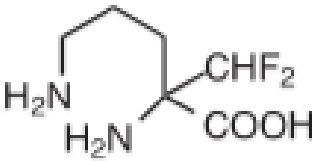
- Therapeutic application:
- ✓ against east trypanosomiasis
- ✓ as prophylactic
- ✓ in sleeping sickness
- ✓ short term treatment & prophylaxis of African trypanosomiasis



Suramin Sodium

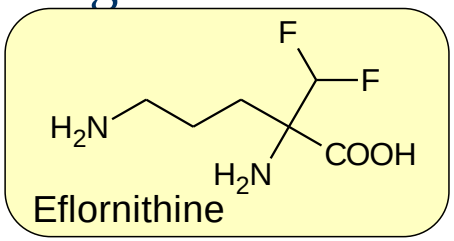
Di-Amino/Amino-Acid Analogue: Eflornithine

- Chemistry: ornithine analogue
- ✓ α-amino acid analogue; di-amino derivative:
- ✓ Di-Fluoro-Methyl Ornithine (DFMO)
- ✓ zwitter ion



Eflornithine

- MOA: suicide inhibitor of Ornithine DeCarboxylase (ODC)
- ✓ ODC: pyridoxal phosphate depending enzyme
- ✓ ODC: rate determining enzyme in synthesis of polyamine
- ✓ alkylation of Cys360 in ODC: how?: next slide.
- ✓ blocks synthesis of putrescin
- ✓ enters CNS readily: via amino acid transport system
- Therapeutic application:
- ✓ against African trypanosomiasis & not against east trypanosomiasis



Eflornithine

Ornithine DeCarboxylase (ODC)

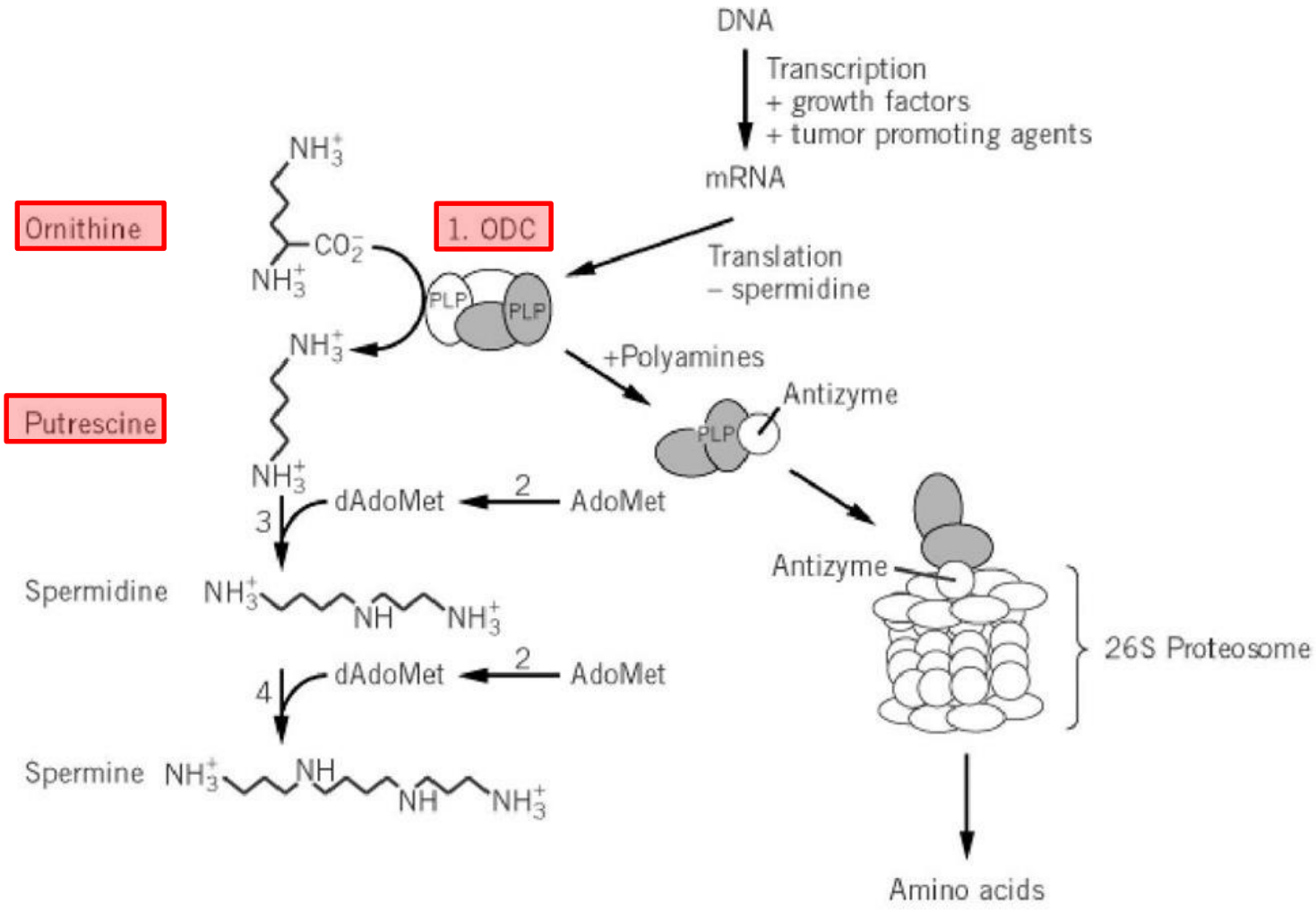
- Rate limiting enzyme in biosynthesis of polyamines
- ✓ polyamines: required in regulation of DNA synthesis & cell proliferation
- ✓
- Polyamines:
- ✓ putrescine $H_2N\text{-}(CH_2)_4\text{-}NH_2$ biosynthesized from ornithine

Which in turn leads to the formation of spermidine & spermine

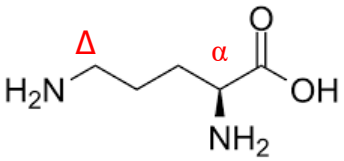
- ✓ spermidine: $H_2N\text{-}(CH_2)_4\text{-}NH\text{-}(CH_2)_3\text{-}NH_2$
  in almost all living species

- ✓ spermine: $H_2N\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_4\text{-}NH\text{-}(CH_2)_3\text{-}NH_2$
  is less common in prokaryotes

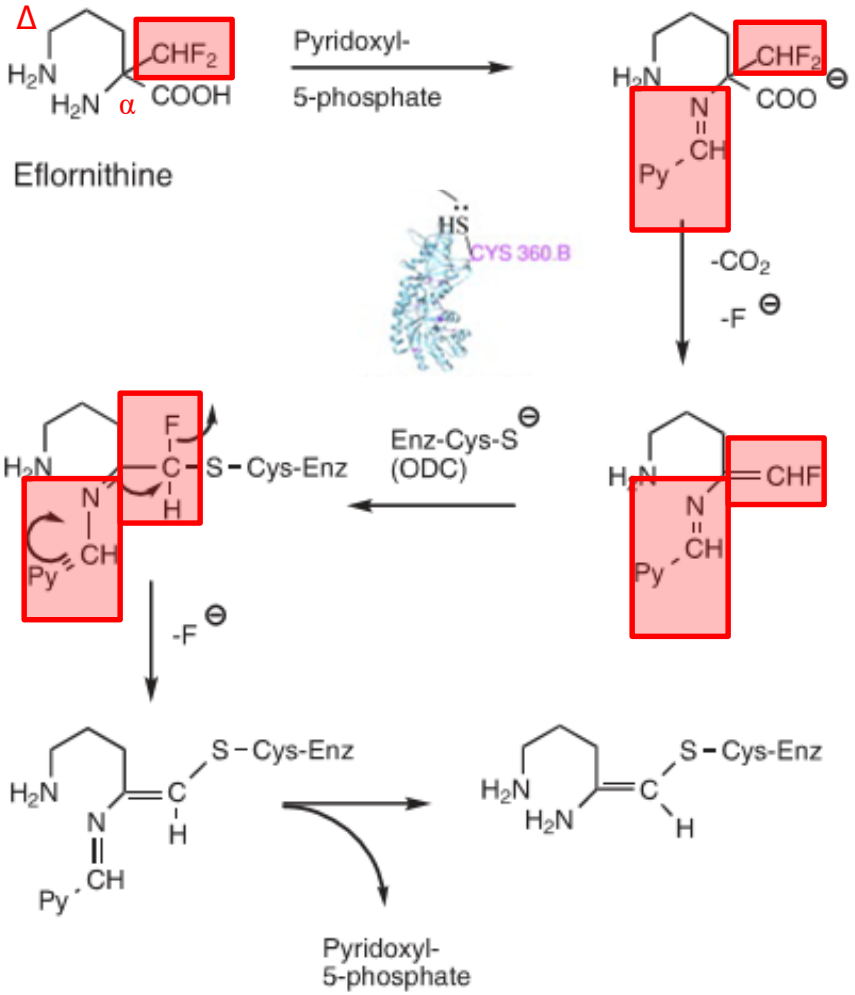
Ornithine to Putrescine by Ornithine Decarboxylase Using PLP

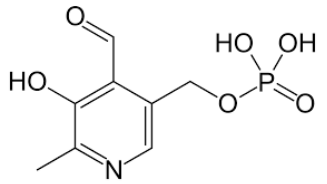


Mechanism of Inhibition for Ornithine DeCarboxylase by Eflornithine



Ornithine



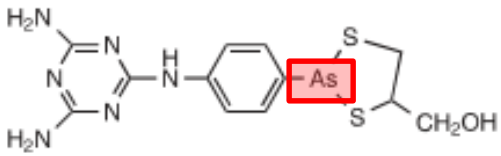


pyridoxal phosphate
= PLP

Figure 32.6 Inhibition of ornithine decarboxylase (Enz-Cys-SH) by eflornithine.

Arsenic Compound: Melarsoprol

- Chemistry: organo-arsenical:
- ✓ trivalent arsenic & tri-amino-triazine
- ✓ water soluble: highly ionic: not cross BBB
- MOA: trivalent arsenic reacts with sulfhydryl (Cys) containing Pr:



Melarsoprol

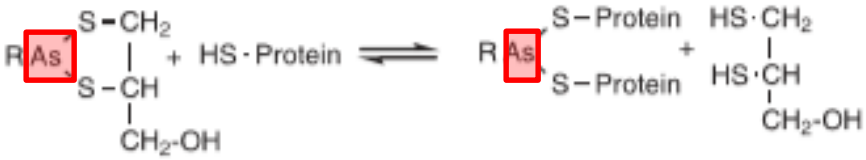


Figure 32.8 Mechanism of action of trivalent arsenic compounds with trypanosoma organism.

- ✓ inhibitor of trypanothione reductase & pyruvate kinase
- Must be monitored for As toxicity
- Therapeutic application:
- ✓ meningo-encephalitic trypanosome
- ✓ first choice in tx of second stage of African trypanosomiasis

Arsenic Compound: Melarsoprol Trypanothione Complex

- MOA:

✓ trivalent arsenic (As) reacts with sulfhydryl (-SH) in Cys containing Prs

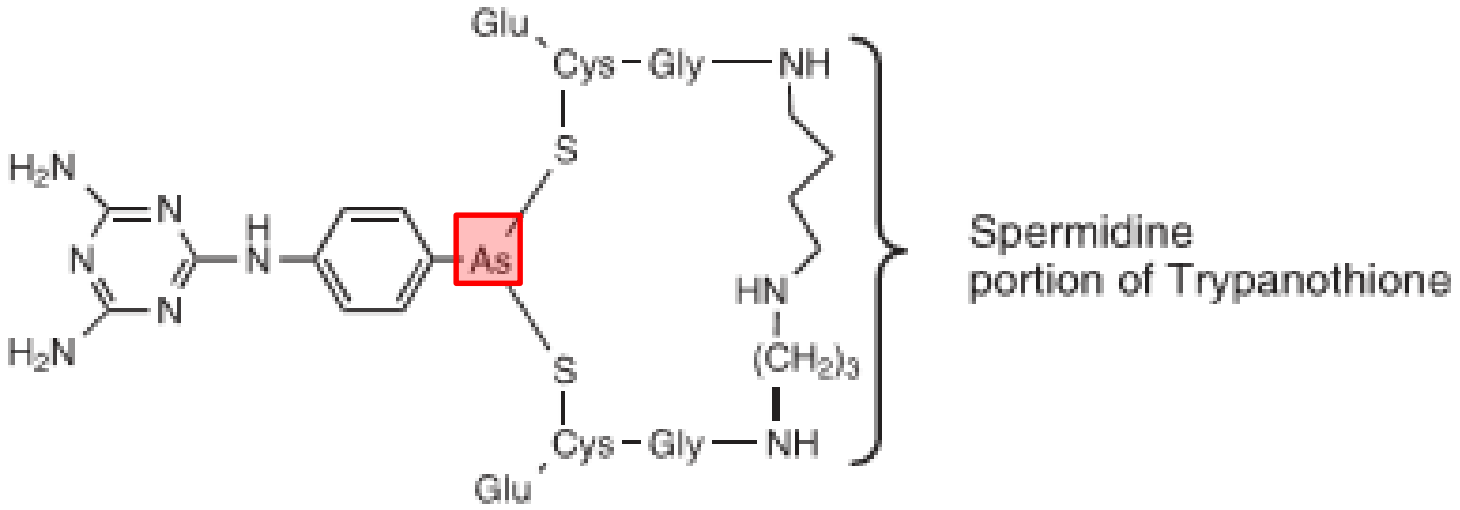
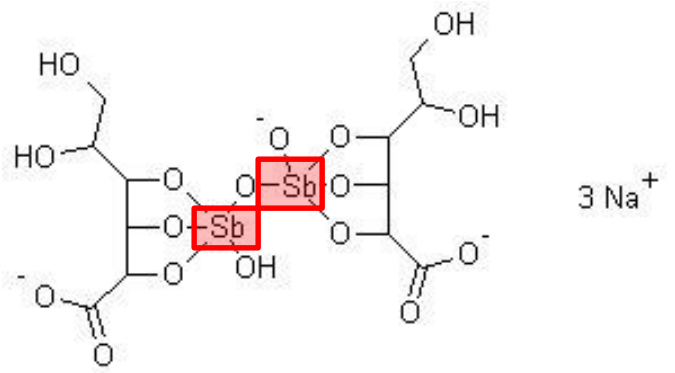


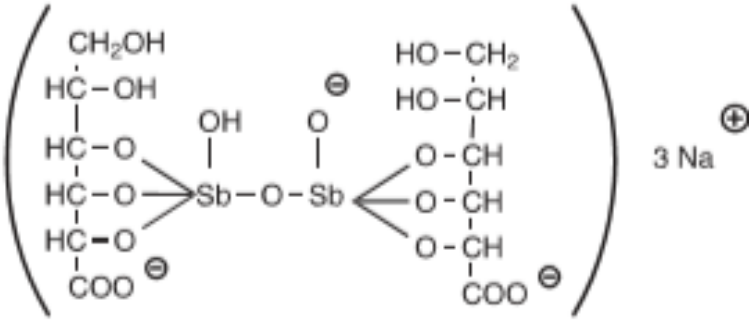
Figure 32.9 Structure of melarsoprol trypanothione complex.

Antimony (Sb) Compound: Sodium Stibo-Gluconate = Meglumine Antimonate

- Chemistry: organo-stibo compound:
- ✓ penta-valent antimony (Sb)
- Water soluble: injection form



- MOA: inhibition of glycolytic enzymes
- ✓ inhibit bioenergetics process; inhibit glycolytic enzymes
- ✓ inhibition of ATP / GTP formation
- Must be monitored for Sb poisoning

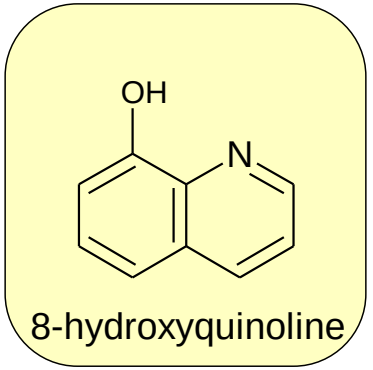


Sodium stibogluconate

- Therapeutic application:
- ✓ Most forms of leishmaniasis

Quinolinic Antiprotozoals

- Amebicide in intestinal forms



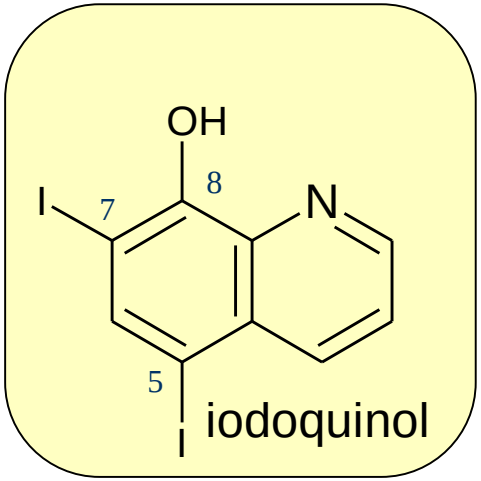
- Iodoquinol:

✓ 5,7-di-iodo-8-hydroxy-quinoline: broader spectrum:

✓ poor GI absorption

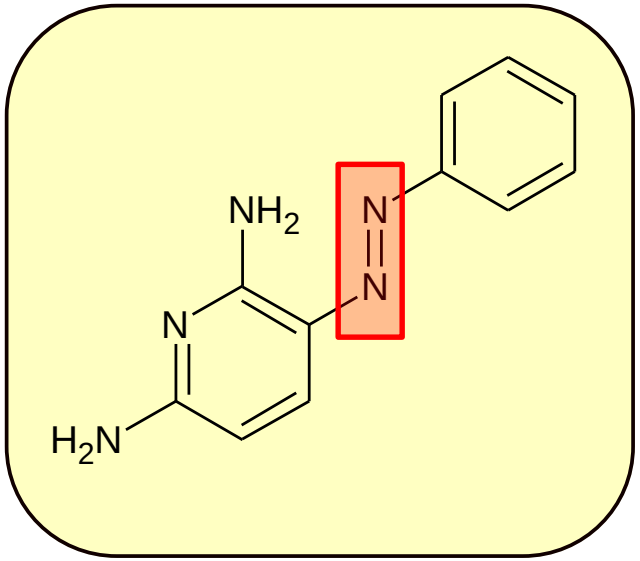
✓ concentrated in intestinal lumen

✓ against Entamoeba histolytica



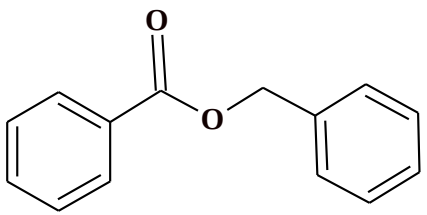
Azo-Pyridine as Anti-Protozoals

- Phenazopyridine
- MOA: ?
- Works as anti-inflammatory NSAIDs
- Clinical indication: in urinary tract infection

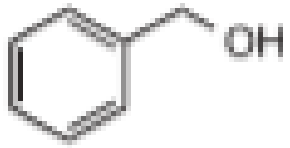


Anti-Ectoparasitic Infections: Antiscabious & Antipedicular (Anti-Lice) Agents

- Benzyl benzoate: scabicide (topical)

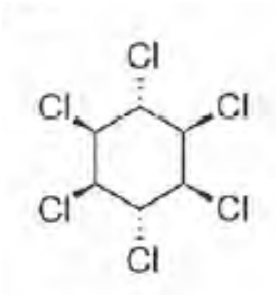


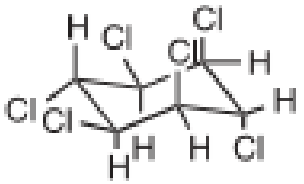
- Benzyl alcohol:
- MOA: affect respiratory system of insect



Benzyl alcohol

- Lindane: hexa-chloro-cyclohexane
- ✓ MOA: CNS stimulatory action:
- ✓ blocks GABA: neurotoxic properties
- ✓ as shampoo & lotion

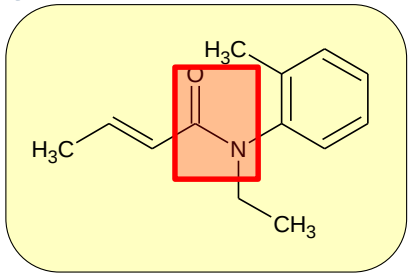




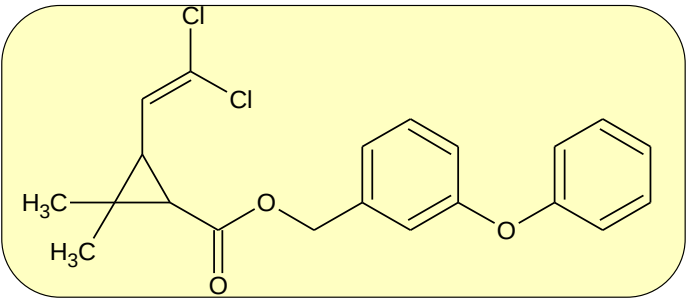
γ-Benzene hexachloride (Lindane)

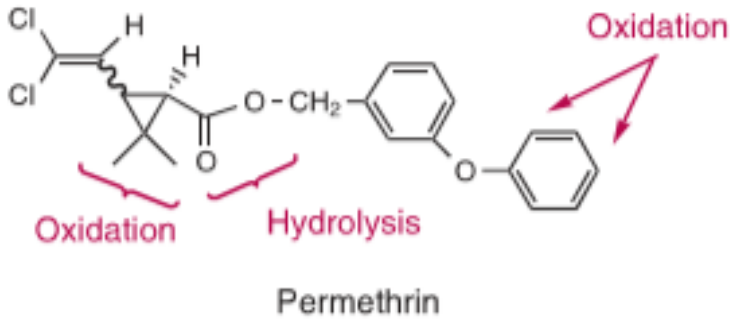
Anti-Ectoparasitic Infections: Antiscabious & Antipedicular (Anti-Lice) Agents- Contd.

- Crotamiton:
- MOA: rapid excitation of nervous system of insect
  - ✓ prolonged excitation: paralysis
  - ✓ relieves caused itching



- Permethrin:
- MOA: nerve Na^+ channel toxins: regulates polarization of cell membrane
  - ✓ slows the rate of inactivation of Na^+ channel: prolong open time
  - ✓ against lice & scabies mice
  - ✓ stereo-specific





Permethrin

Pyrethroid Derivatives

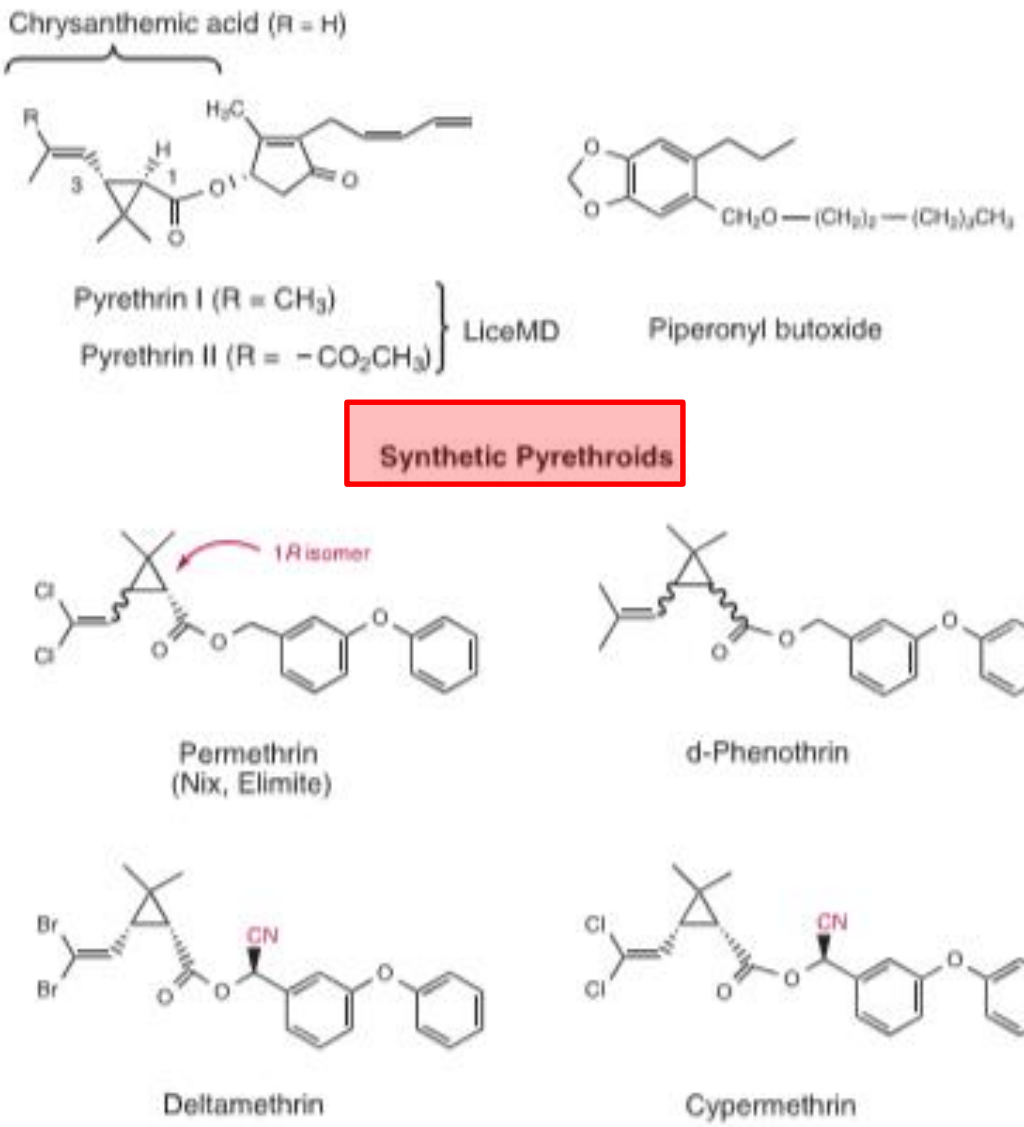


Figure 32.22 Structures of the naturally occuring pyrethrins, the synergist piperonyl butoxide, and the pyrethroid derivatives.

Metabolism of Permethrin