Anthelmintic Agents
= Anthelmintics

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CHAPTER 32

Drugs Used to Treat Parasitic Infections

Thomas L. Lemke

TREATMENT OF HELMINTH INFECTIONS:

- Albendazole
- Ivermectin
- Mebendazole
- Moxidectin
- Praziquantel
- Pyrantel pamoate

Types of Helminths

- Platyhelminths:

✓ cestodes(tapeworm): taenia
✓ trematodes(flukes): schistosoma

- Nematohelminths:

✓ ascaris
✓ strongyloides

- True round worms:

✓ hookworm
✓ pinworm
✓ wuchererria bancrofti
✓ onchocerca

Chemical Classification for Anthelmintic agents

- Benz-imidazoles:

✓ albendazole

✓ mebendazole

✓ thiabendazole

- Tetra-hydro-iso-quinoline: praziquantel
- Tetra-hydro-quinoline: oxamniquine
- Tetra-hydro-pyrimidine: pyrantel
- Levamisole
- Piperazine: piperazine & Di-Ethyl Carbamazine(DEC)
- Lactone: ivermectin, moxidectin
- Benzamide: niclosamide

Benzimidazole Anthelmintics

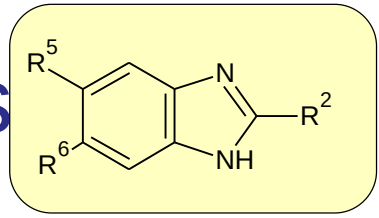
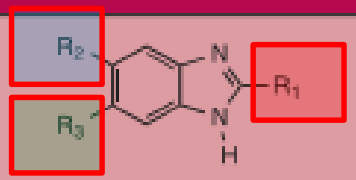
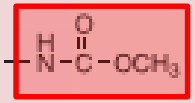
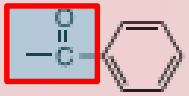
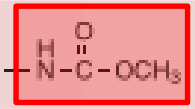
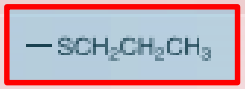
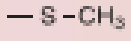
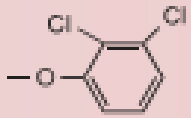
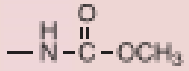
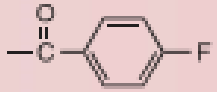


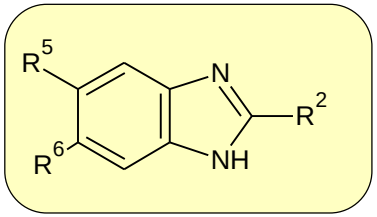
Table 32.7 Benzimidazole Anthelmintics

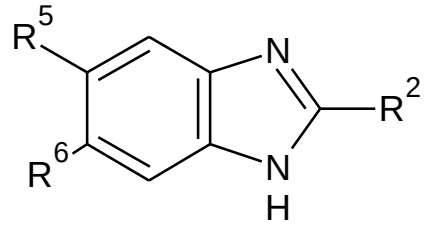


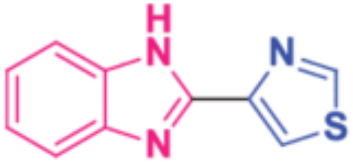
Drugs	Trade Name	R_1	R_2	R_3
Mebendazole	Emverm Vermox			H
Albendazole	Albenza			H
Triclabendazole	Egaten[a] Fasinex[b]			Cl
Fenbendazole	Several brand names[b]			H
Flubendazole	Several brand names[b]			H

[a]Egaten has recently been shown to be useful for treatment of fasciolasis by WHO.
[b]Used in veterinary practice for protection and treatment of parasite and worm infections.

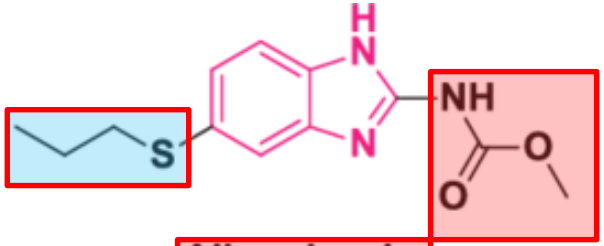
Benzimidazoles as Anthelminthics



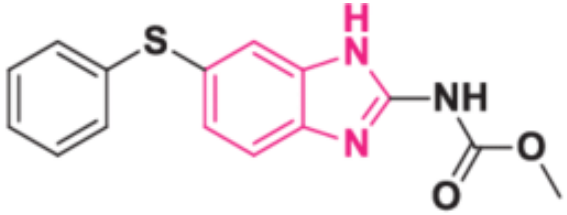




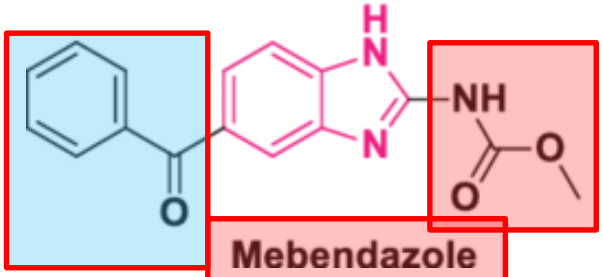
Thiabendazole



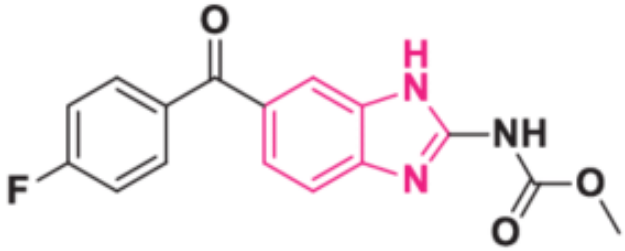
Albendazole



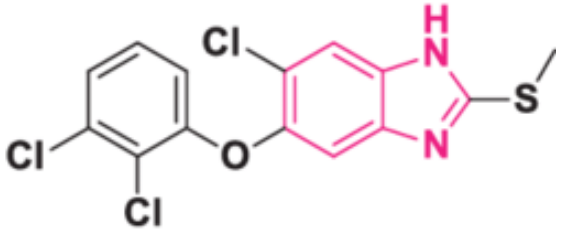
Fenbendazole



Mebendazole



Flubendazole



Triclabendazole

MOAs for Benzimidazole Anthelmintics

- Broad spectrum on intestinal helminths

1- inhibition of fumarate reductase:

✓ responsible enzyme for oxidation of NADH to NAD

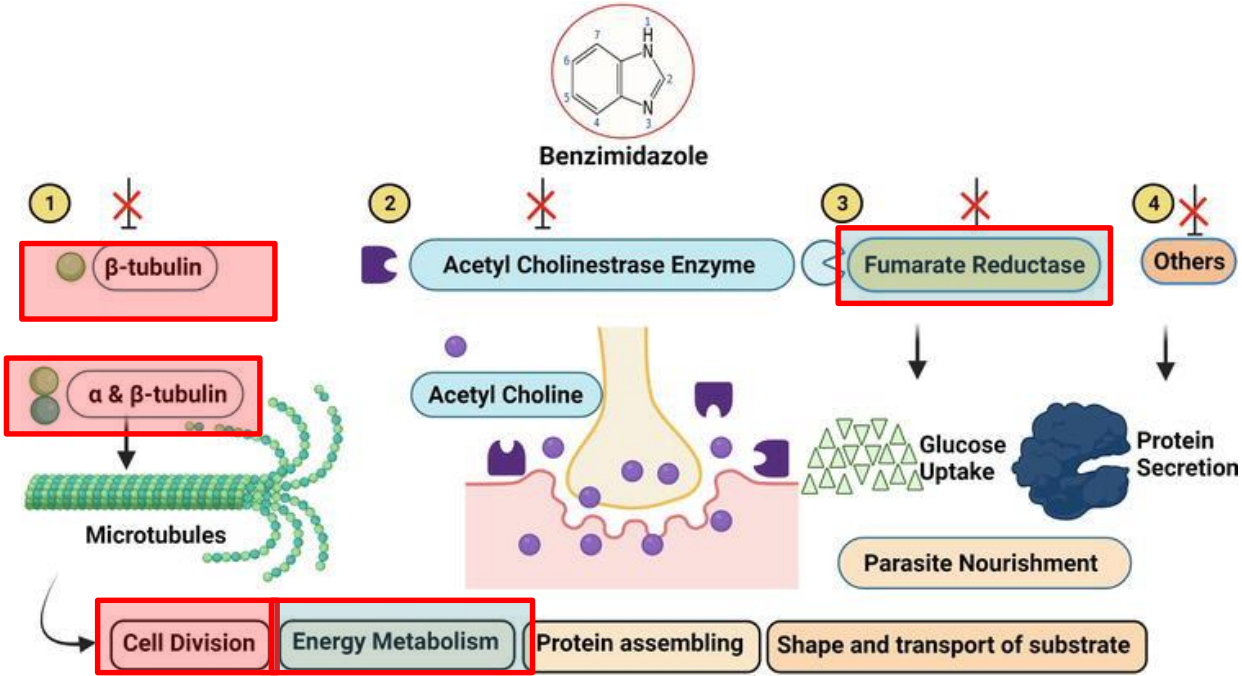
✓ which uncouples oxidative phosphorylation for ATP production

2- Prevention of tubulin polymerization:

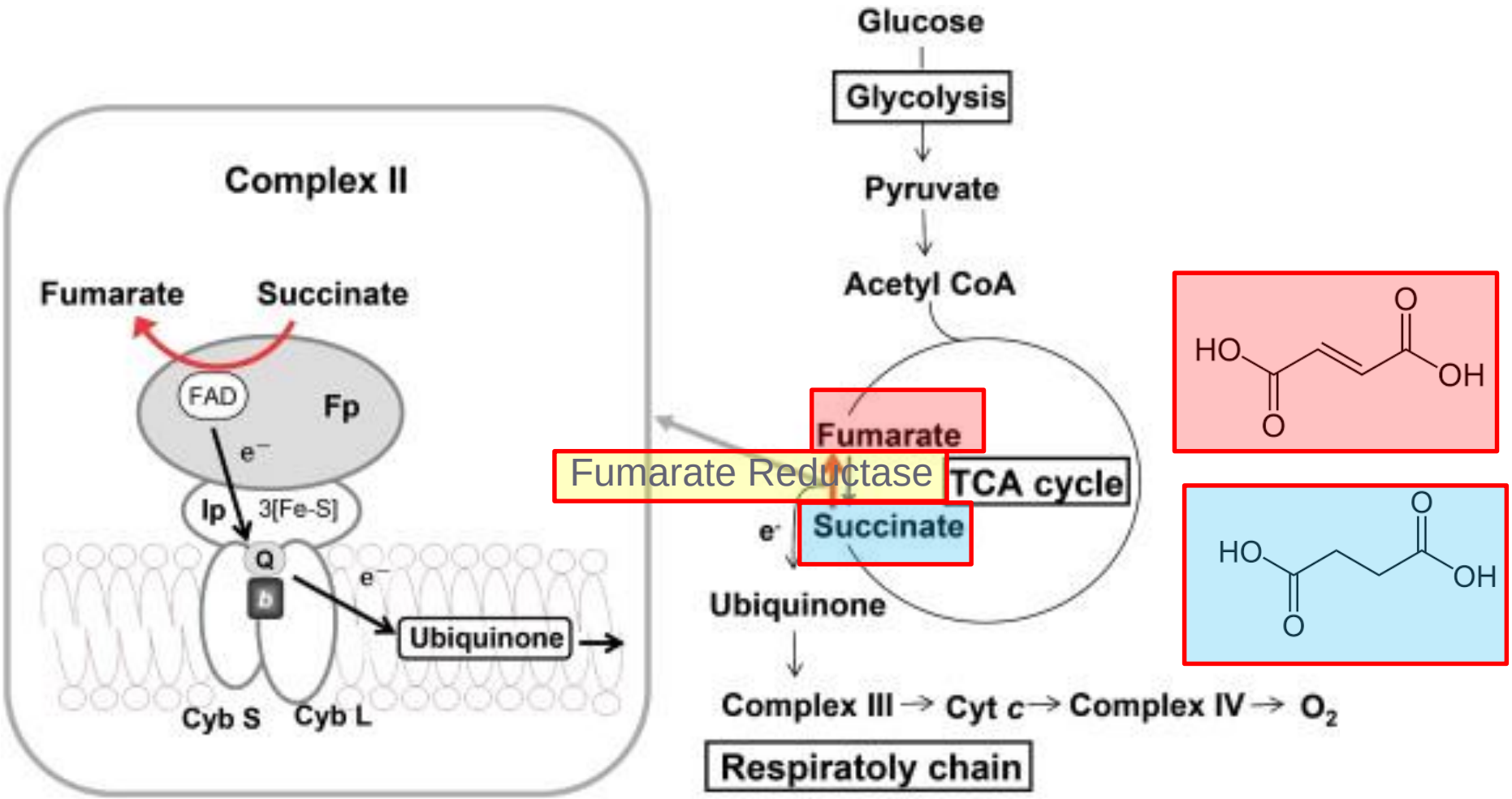
✓ prevents self association of tubulin subunits

✓ create a capping of microtubule at associating or polymerizing end

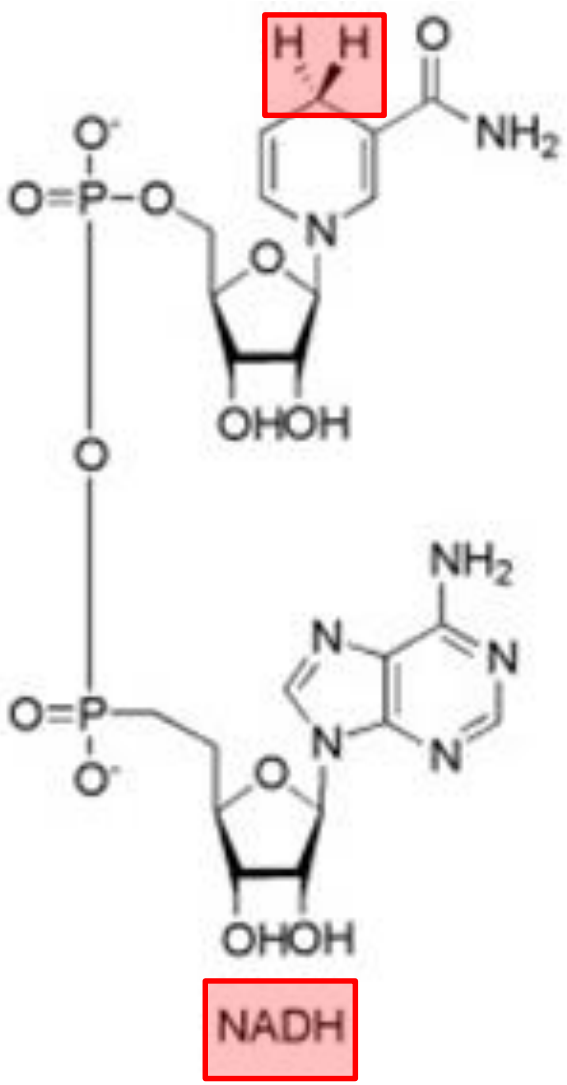
✓ hence microtubule dissociation from opposite end with a net loss of length

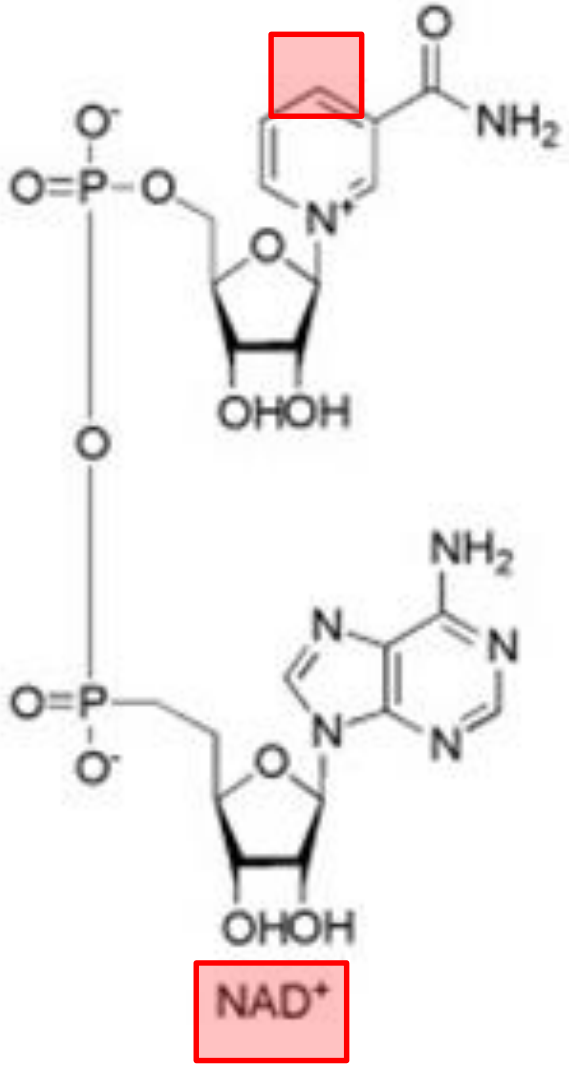


Fumarate Reductase as a Functional enzyme in Vitality of Helminths

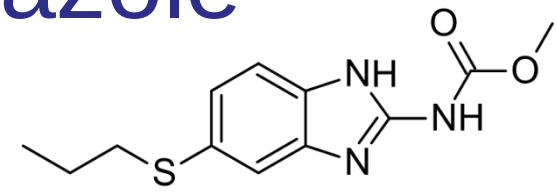


Oxidation of NADH to NAD





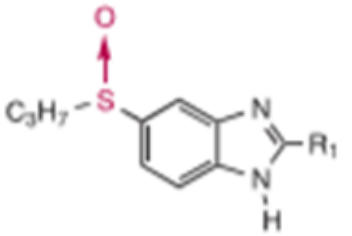
Benzimidazole: Albendazole



- Chemistry:
- Metabolism: through FMO CYP related:

sulfur mono-oxide= sulfone: active metabolite

- MOA: …



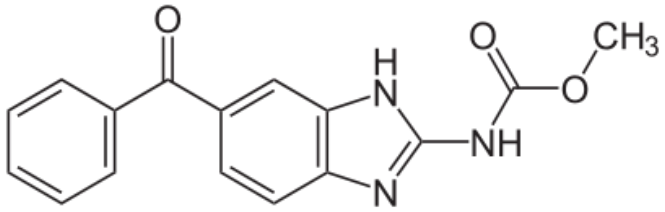
Albendazole sulfoxide (active)

- Single dose for ascariasis & hook worm infections
- Multiple dose for pinworm
- Therapeutic application:

✓ against *echinococciasis*

- Enhancing oral absorption with fatty meals: ?

Benzimidazole: Mebendazole



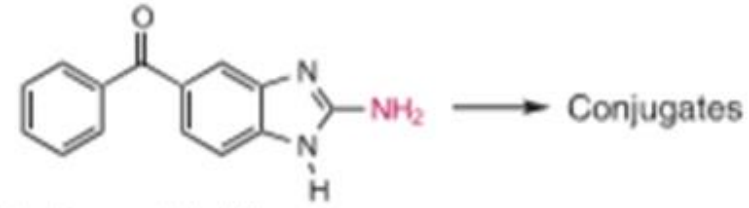
- Chemistry:
- Metabolism:

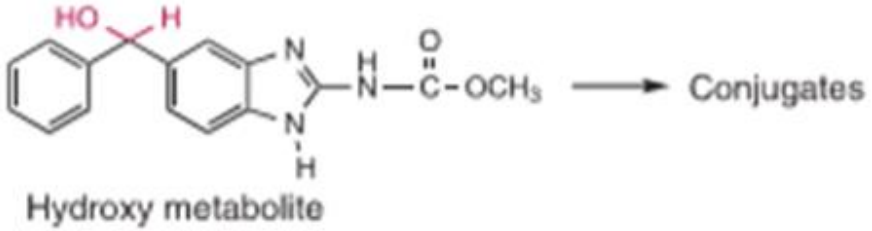
✓ Phase I:

hydrolysis of amide: deacetylation

reduction of ketone

✓ phase II: conjugation step





✓ MOA:

✓ interfering in glucose uptake

✓ glycogen storage depletion

Metabolism of Benzimidazoles

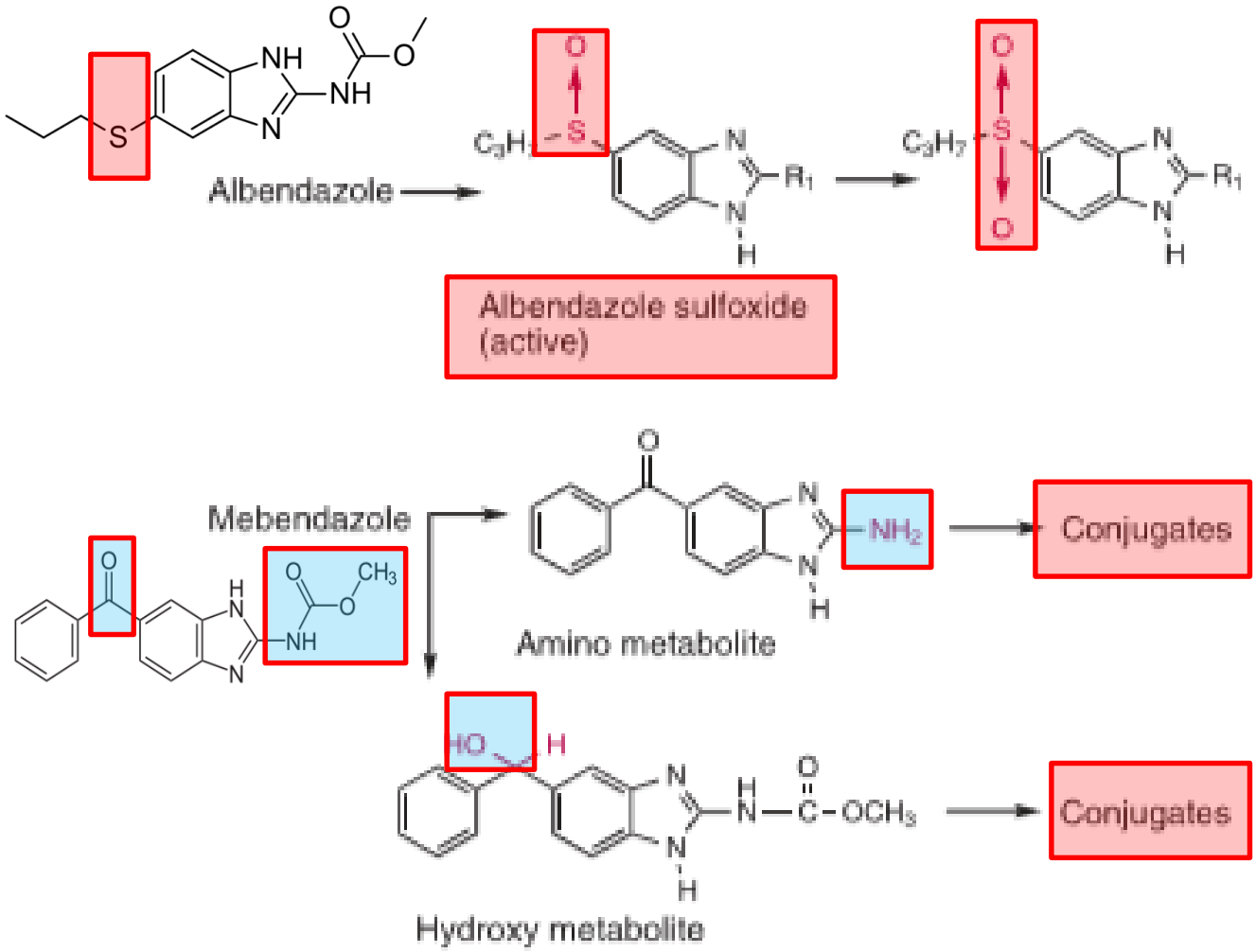
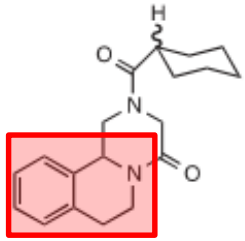


Figure 32.20 Metabolism of benzimidazoles.

Tetra-Hydro-Iso-quinoline: Praziquantel (PZQ)



Praziquantel
(Biltricide)

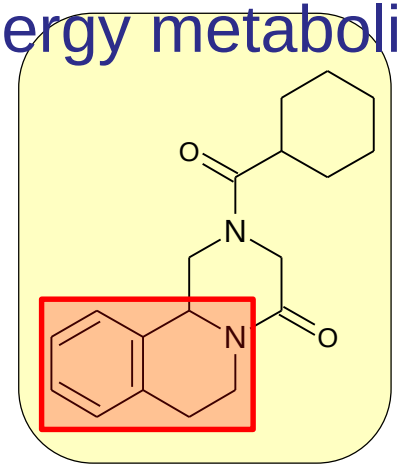
- Chemistry: iso-quinoline derivative

- Metabolism: next slide
- MOA:

✓ in/direct Ca^{2+} redistribution: muscle contraction & paralysis

✓ inhibit phospho-inositide metabolism

✓ affects glycogen content & energy metabolism



- Therapeutic application:

✓ against cestode & trematode

✓ against *schistosomiasis*

Metabolism for Praziquantel (PZQ)

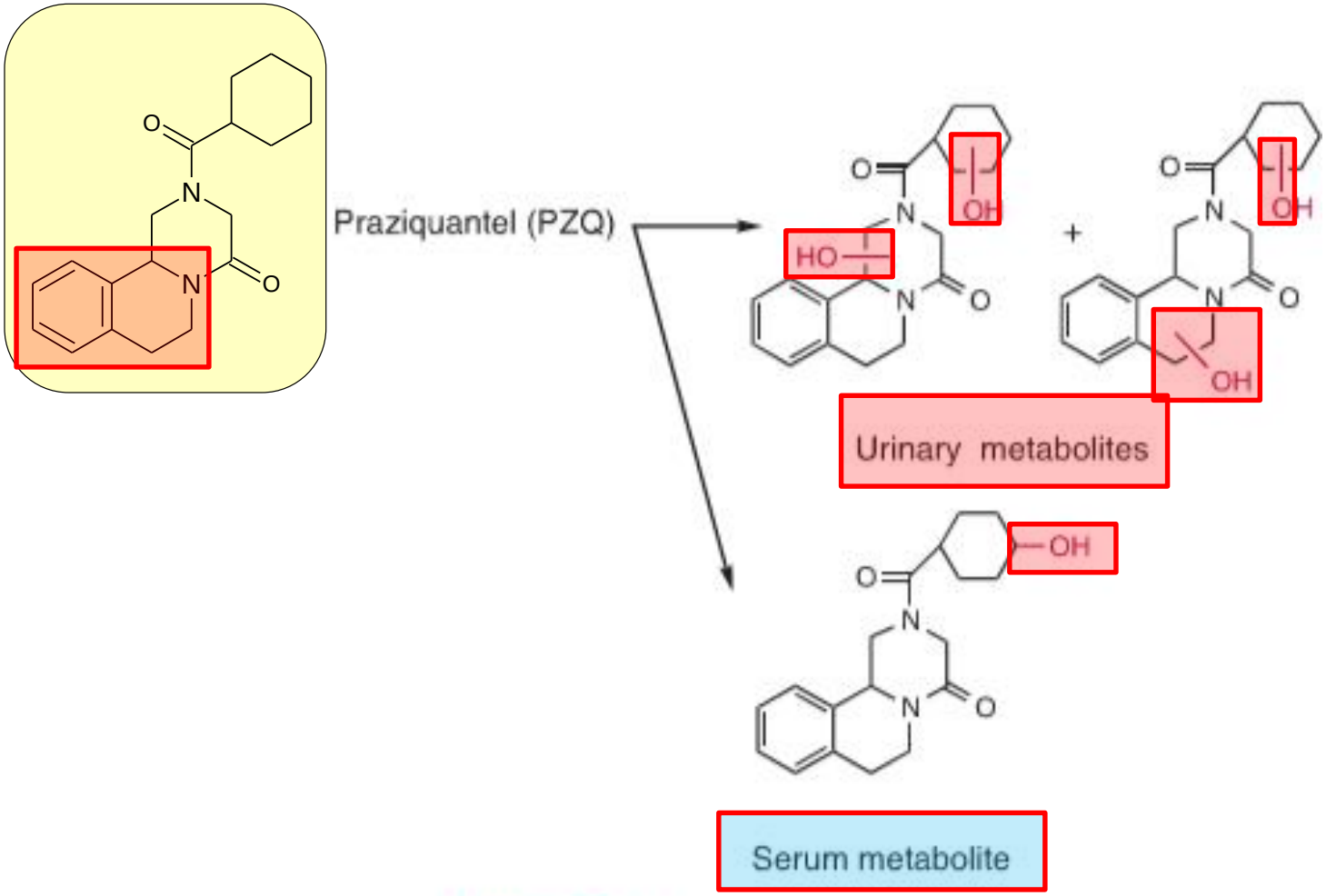
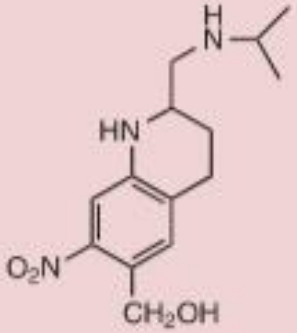


Figure 32.21 Metabolism of praziquantel (PZQ).

Tetra-Hydro-Quinoline: Oxamniquine

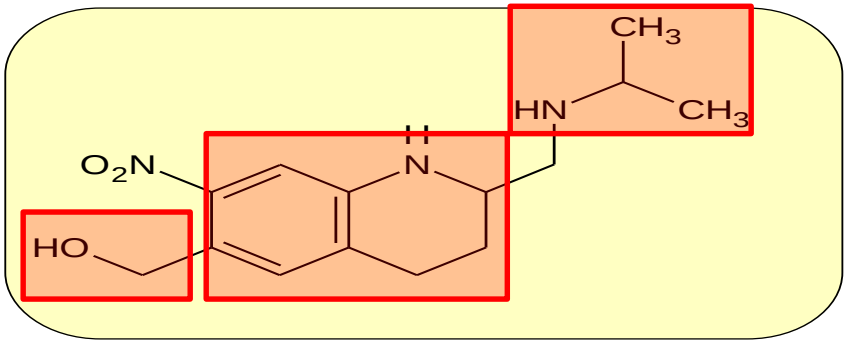
MOA: inhibit DNA, RNA & protein synthesis

OXAMNIQUINE



Oxamniquine

Oxamniquine was previously available with a spectrum of activity similar to that of praziquantel. The drug has been discontinued in the United States. The drug is listed in the WHO Model List of Essential Medicines 20th List (March 2017) as an antischistosomal backup when praziquantel treatment fails.

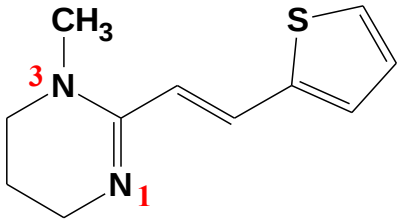


Tetra-Hydro-pyrimidine: Pyrantel Pamoate

- Chemistry:

✓ pamoate salt: quite in-soluble: not readily absorbed: benefit?

✓ tartrate salt: water solubility

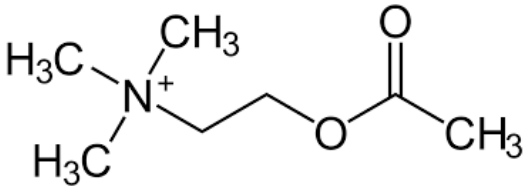


- MOA:

✓ depolarizing NMBA: activate nicotinic receptors

✓ inhibit cholinesterase

✓ gives spastic paralysis



Acetylcholine

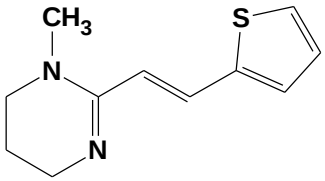
- Therapeutic application:

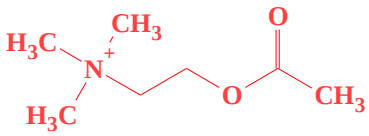
✓ against pinworms (considered as drug of choice)

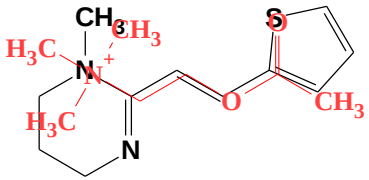
✓ against hookworm & roundworms (ascariasis)

✓ with piperazine!!! is a wrong medication

Acetylcholine Esterase Inhibitor as Second Mechanism of Action for Pyrantel







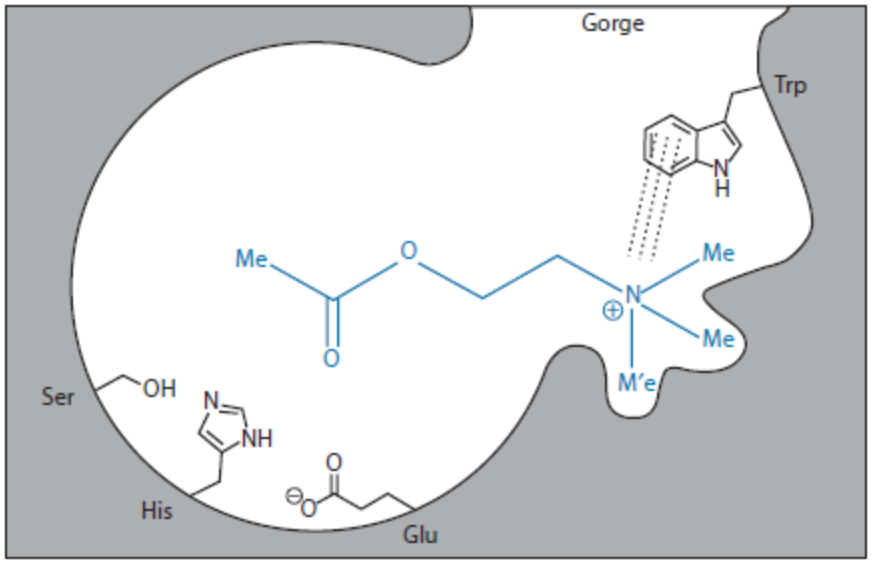
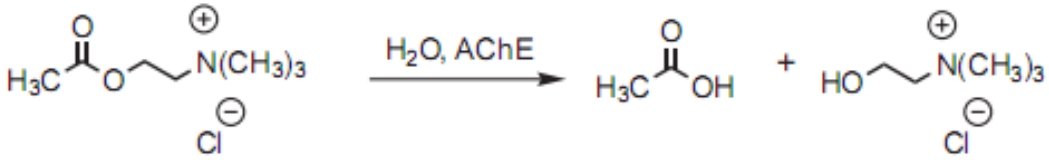
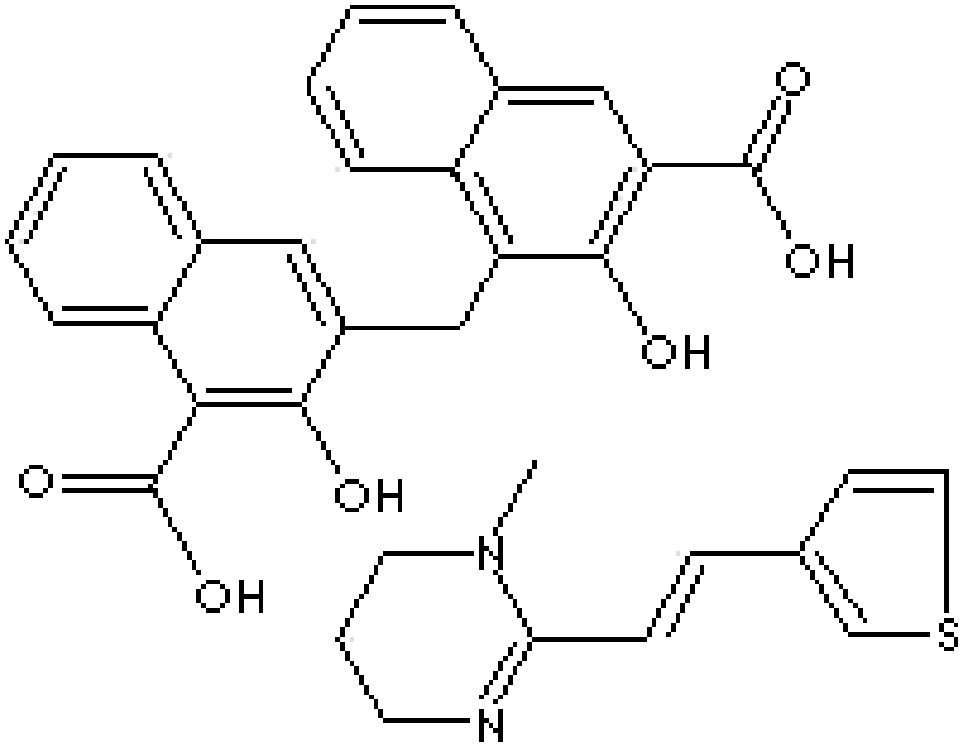


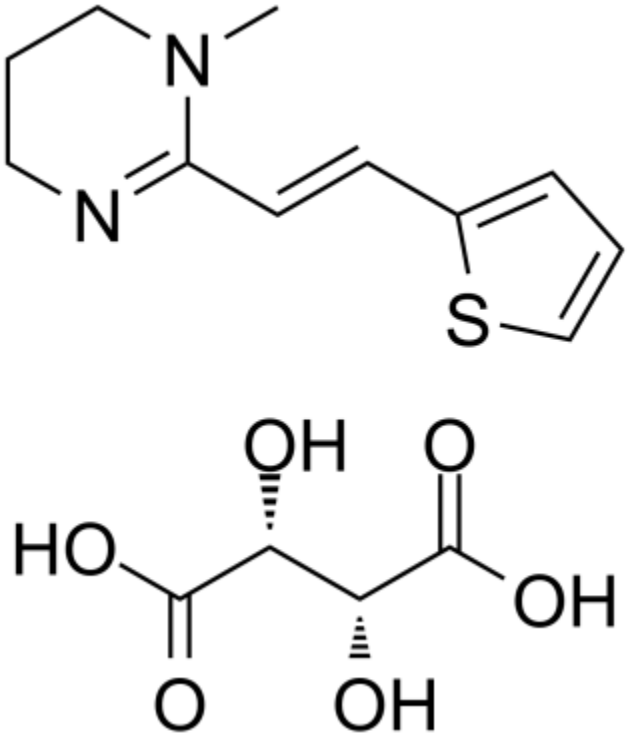
FIGURE 22.42 Key amino acid residues within the active site.



Pyrantel in Two Types of Salts: as Pamoate Salt & Tartrate Salt



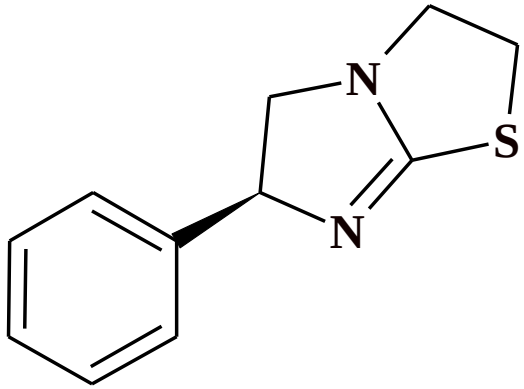
Pamoate Salt



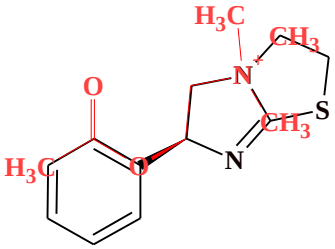
Tartrate Salt

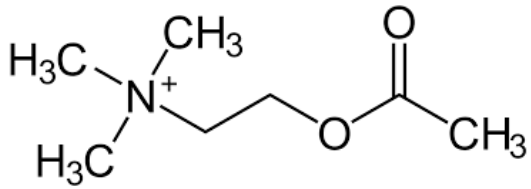
Levamisole

- Chemistry:



- Withdrawn from FDA since 2000
- MOA: acetylcholine agonist on nAChR in nematodes



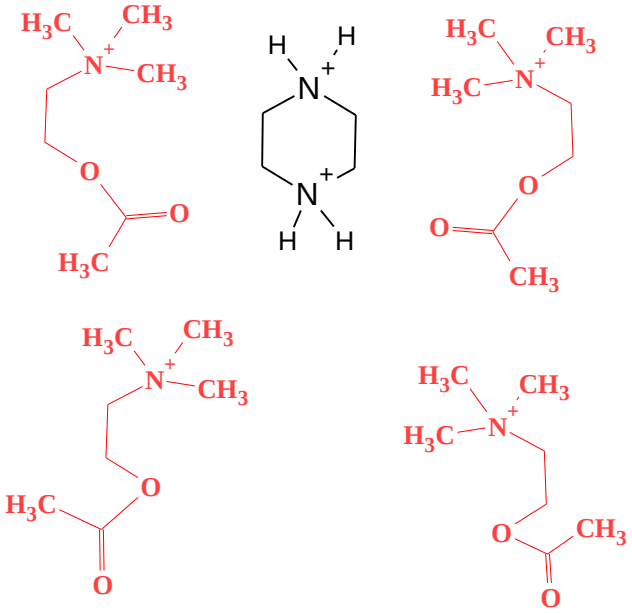


Acetylcholine

Piperazine Anthelmintics: Piperazine

- Chemistry:

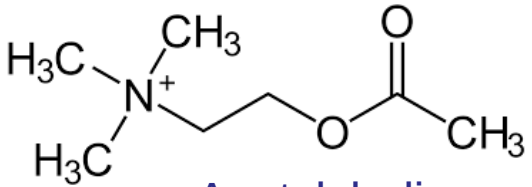
✓ citrate salt



piperazine citrate

- MOA:

✓ block the response of worm muscles to acetylcholine



Acetylcholine

- Therapeutic application:

✓ against pinworm & roundworm(nematodes)

Piperazine Anthelmintics: Di-Ethyl-Carbamazine (DEC)

- Chemistry:

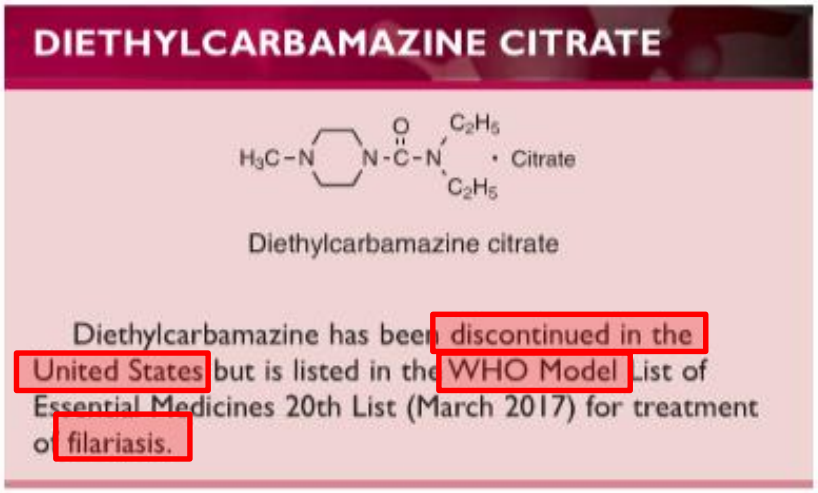
✓ citrate salt

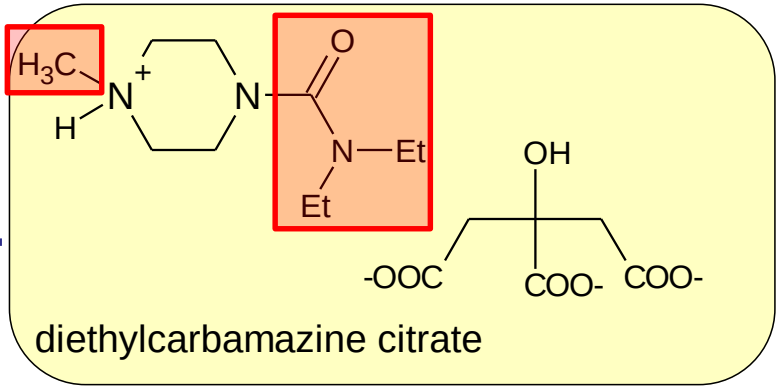
- Selective anthelmintic activity: filaricide:

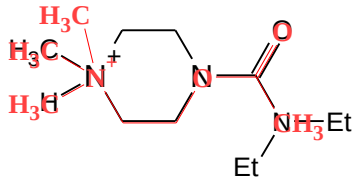
✓ against *filariasis*, *ascariasis*, *onchocerciasis*

- Metabolites: ?
- MOA: !?: Rapid action

✓ three proposed mechanisms: …

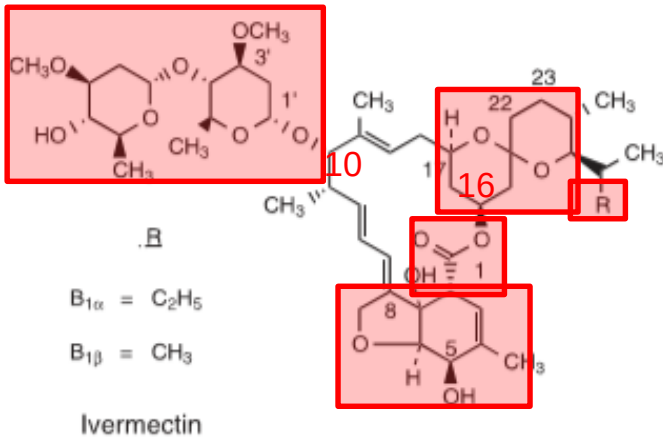






Lactone: Dihydro/Ivermectin (IVM)

- Source: extracted from *Streptomyces avermitilis*
- Chemistry: 16 membered macrocyclic lactone: $B_{1\alpha}$:$B_{1ß}$(80:20)

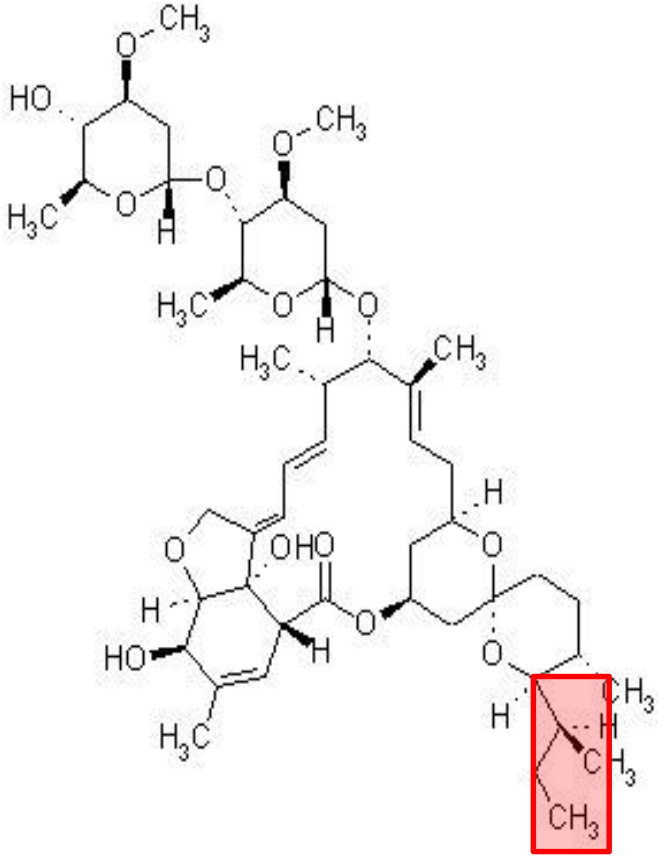


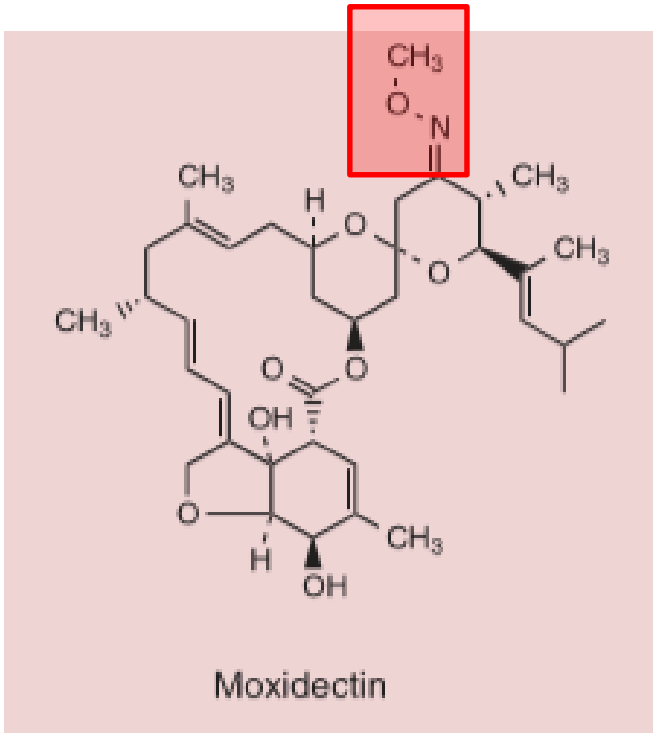
- ✓ consider C23 substitute
- MOA:
- ✓ reduce motility of *microfilaria*:
- ✓ allows host cytotoxic cells to adhere to parasite
- ✓ acts as GABA agonist: induce Cl^- influx:
- ✓ lead to hyperpolarization & muscle paralysis
- ✓ irreversibly bind to Glu gated Cl^- channel: open conformation of gate
- Advantage over DEC (Di-Ethyl Carbamazine)

- Know about efficacy in COVID-19: inhibit host nuclear transport Prs which are part of key intracellular target of virus

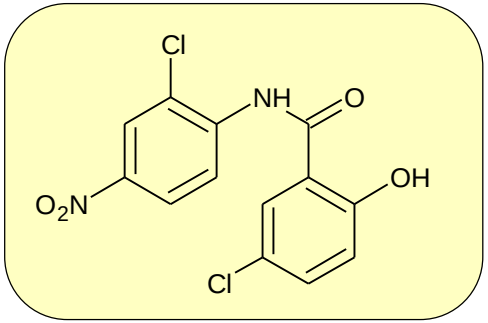
Lactones: Ivermectin & Moxidectin

- Novel derivative: moxidectin





Benzamide: Niclosamide



- Potent taenicide:

✓ rapid disintegration of worm segments

- MOA:

✓ uncoupling oxidative phosphorylation or stimulation of ATPase activity

✓ might bind to DNA & make DNA damage