LNCT GROUP OF COLLEGES

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Subject: Medicinal Chemistry-III (BP 601T)
Unit: IV
Topic: ANTHELMINTICS

Anthelmintic Drugs

- Infections with helminths, or parasitic worms, affect more than two billion people worldwide.
- Anthelmintics are drugs that either kill (**vermicide**) or expel (**vermifuge**) infesting helminths. Helminthiasis is prevalent globally (1/3rd of world's population harbours them).
- Helminthiasis is **more common in developing countries** with poorer personal and environmental hygiene.
- **Helminthiasis is rarely fatal, but is a major cause of ill health.**

Anthelmintic Drugs

- Classification of anthelmintics based on chemical structure
  - **Piperazines: Diethylcarbamazine citrate (DEC), Piperazine citrate.**
  - **Benzimidazoles: Albendazole, Mebendazole, Thiabendazole.**
  - Heterocyclics: Oxamniquine, Praziquantel.
  - **Natural products: Ivermectin**, Avermectin.
  - Vinyl pyrimidines: Pyrantel, Oxantel.
  - **Amide: Niclosamide.**
  - Nitro derivative: Niridazole.
  - Imidazo thiazole: Levamisole.

Diethyl carbamazine citrate (DEC)

- Diethylcarbamazine has a highly selective effect on microfilariae (Mf) at a dose of 2 mg/kg TDS. The most important action of DEC appears to be alteration of Mf membranes so that they are readily phagocytosed by tissue fixed monocytes, but not by circulating phagocytes.
- Use: Used for the treatment of filariasis, tropical eosinophilia, *Loa loa* and *Onchocerca vovulus* infections.
- ADR: ADR is common but not serious. Nausea, loss of appetite, headache, general weakness and dizziness.

Diethyl carbamazine citrate (DEC)

- DEC developed in 1948, and its is the first drug for filariasis.
- DEC absorbed after oral ingestion, well distributed, metabolized in liver and excreted in urine. Excretion is faster in acidic urine. Plasma t½ is around 4-12 hours.

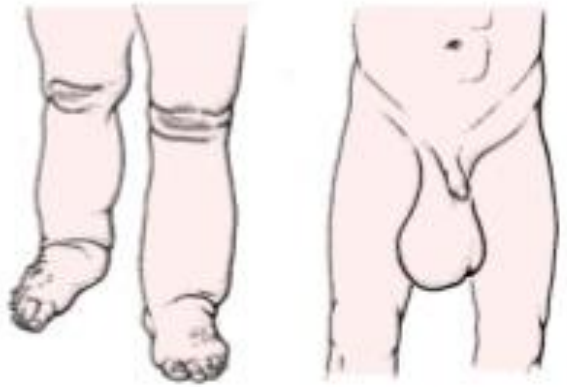
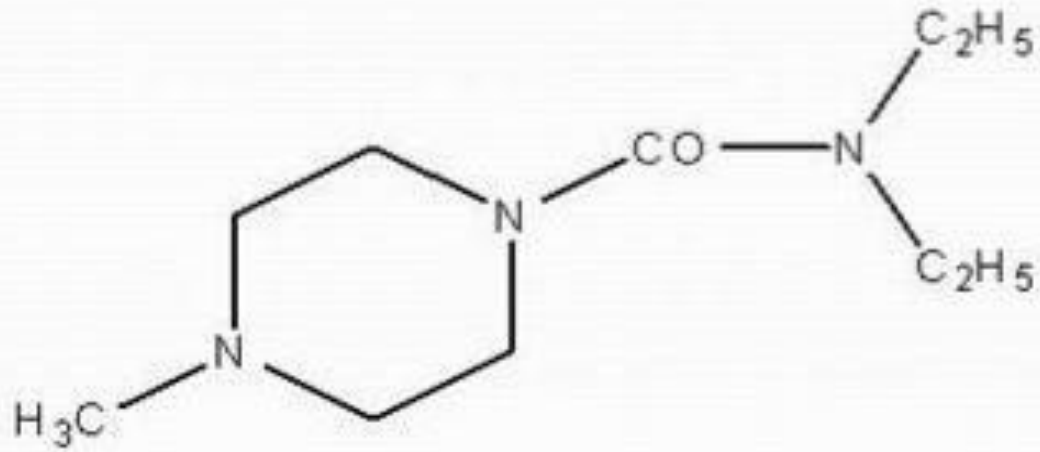


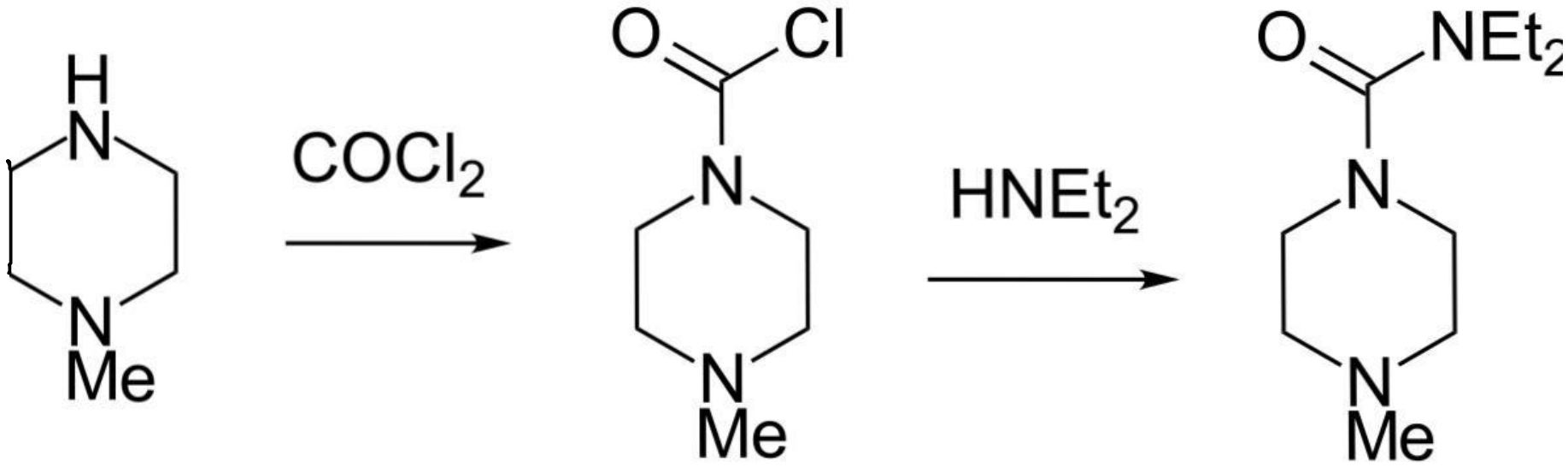
Figure 7 – Staged reduction in girth from baseline to three years and six months post treatment.

DIETHYL CARBAZINE CITRATE

- HETRAZAN
- N,N-diethyl-4-methyl-1-piperazine carboxamide

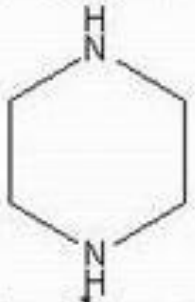


SYNTHESIS



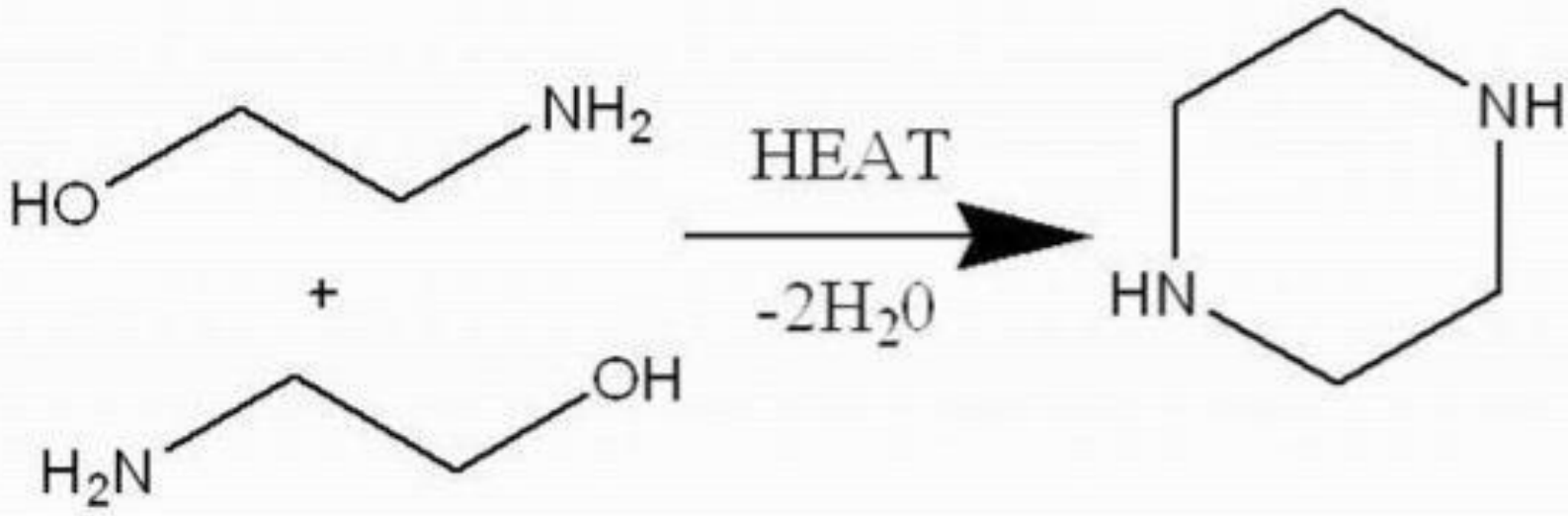
PIPERAZINE CITRATE

- Artheriticine, Dispermin



- MOA: It blocks the response of the ascaris muscle to acetyl choline, causing the flaccid paralysis in the worm, which is dislodged from the intestinal wall and expelled in the feces.
- Highly effective against Ascaris lumbricoides & Enterobius vermicularis.(Round worm & thread worm)

SYNTHESIS

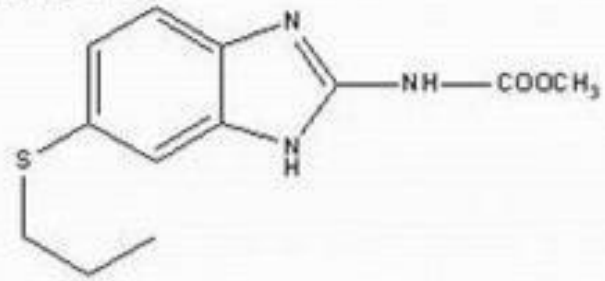


Albendazole

- Albendazole, a broad-spectrum oral anthelmintic agent.
- **MOA is similar to mebendazole.**
- **Uses:**
  - Used for the treatment of ascariasis, trichuriasis, hookworm and pinworm infections
  - Used for the treatment of Hydatid disease, neurocysticercosis, cutaneous larva migrans and visceral larva migrans.
- **ADR:** Mild and transient epigastric distress, diarrhea, headache, nausea, dizziness, lassitude, and insomnia can occur. Produce embryotoxicity , contraindicated to pregnant mother.
- **Dose:** 400 mg/ Oral

ALBENDAZOLE

- Eskazole, Zentel



- Methyl 5-(propylthio)-2-benzimidazole carbamate
- Widely employed throughout the world for the treatment of intestinal nematode function.
- Is effective as a single dose treatment for
  - ❑ Ascariasis
  - ❑ Hookworm infections
  - ❑ Trichuriasis

Mebendazole

- Mebendazole is wide spectrum of anthelmintic activity and a low incidence of adverse effects.

- It is a drug of choice in the treatment of infections by whipworm eggs, pinworm, hookworms, and roundworm.

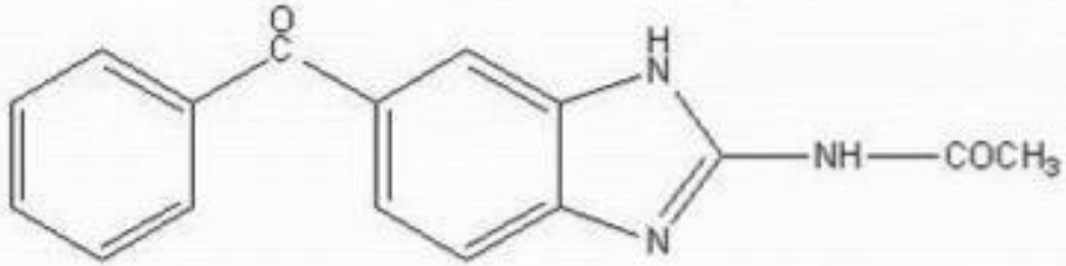
- **Mechanism of action:**
  - Mebendazole probably acts by **inhibiting microtubule synthesis**. Its **bind with parasite 'β-tubulin' and inhibit its polymerization**. In addition mebendazole probably **blocks glucose uptake in parasite and depletes its glycogen stores**.

Mebendazole

- **Adverse effects:**
  - Well tolerated even by patient in poor health.
  - Mild nausea, vomiting, diarrhea, and abdominal pain have been reported infrequently.
  - Mebendazole is teratogenic in animals and therefore contraindicated in pregnancy.
  - It should be used with caution in children younger than 2 years of age because of limited experience and rare reports of convulsions in this age group.

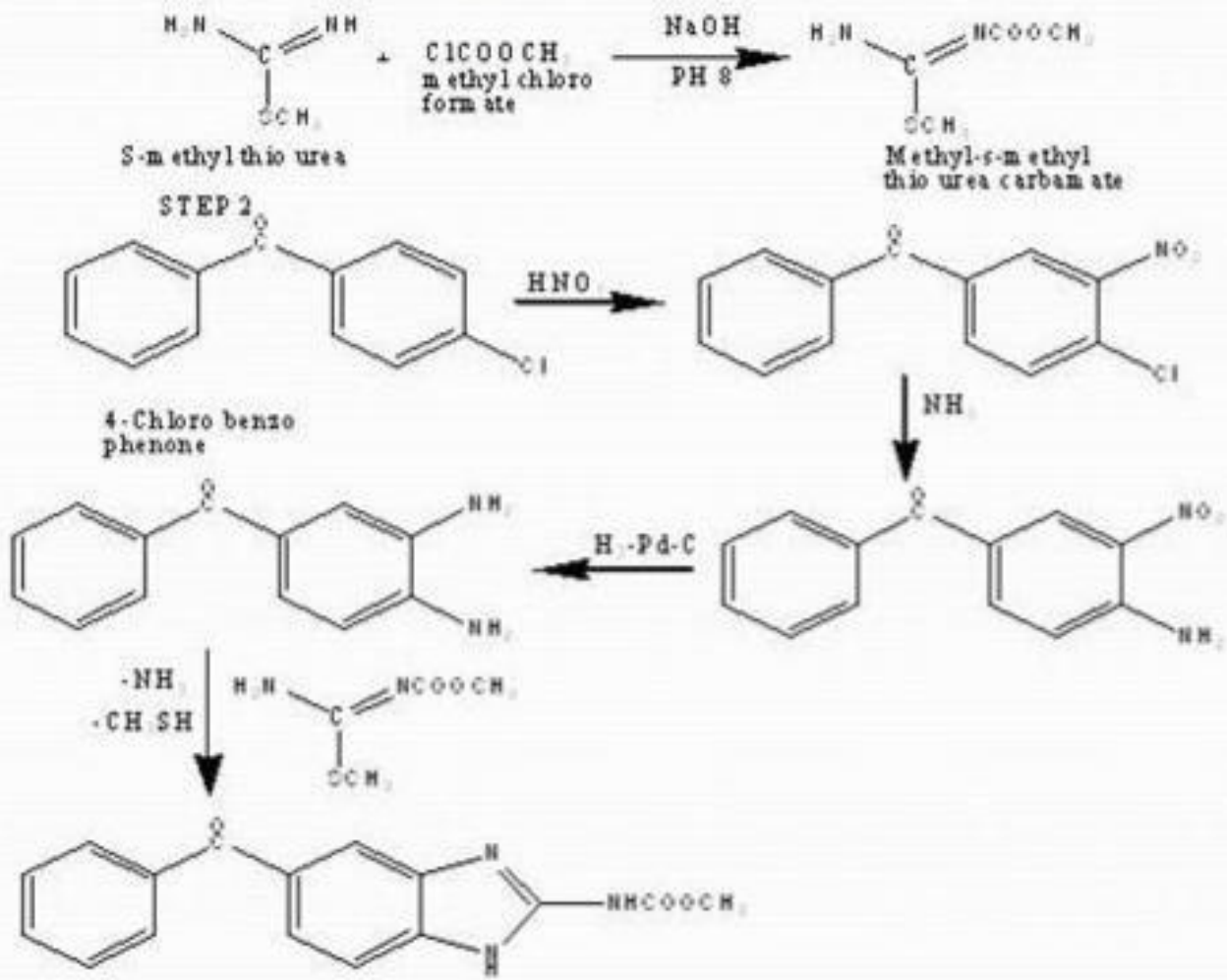
MEBENDAZOLE

- Vermox
- Methyl-5-benzoyl-2-benzimidazolyl carbamate.



- MOA- It irreversibly blocks glucose uptake in susceptible helminths, therby depleting glycogen stored in the parasite.
- It does not affect glucose metabolism in the host.

SYNTHESIS

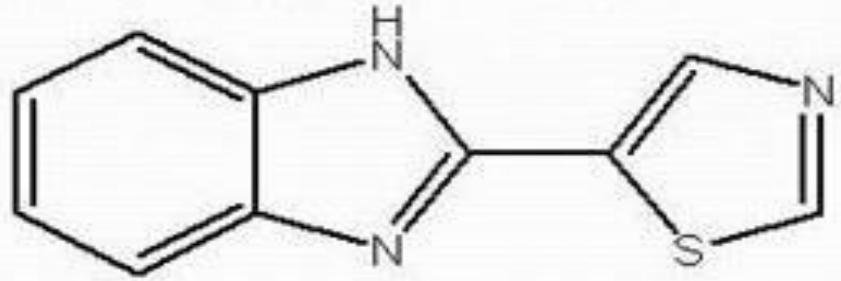

STEP 1
S-methyl thio urea
methyl chloro formate
NaOH
PH 8
Methyl-s-methyl thio urea carbamate
STEP 2
HNO
4-Chloro benzo phenone
NH
H -Pd-C
-NH
-CH SH

USES

- Effective against
- Whip worm (Trichuria)
- Pin worm(Enterobius vermicularis)
- Hook worm
- Ascaris lumbricoides

THIABENDAZOLE

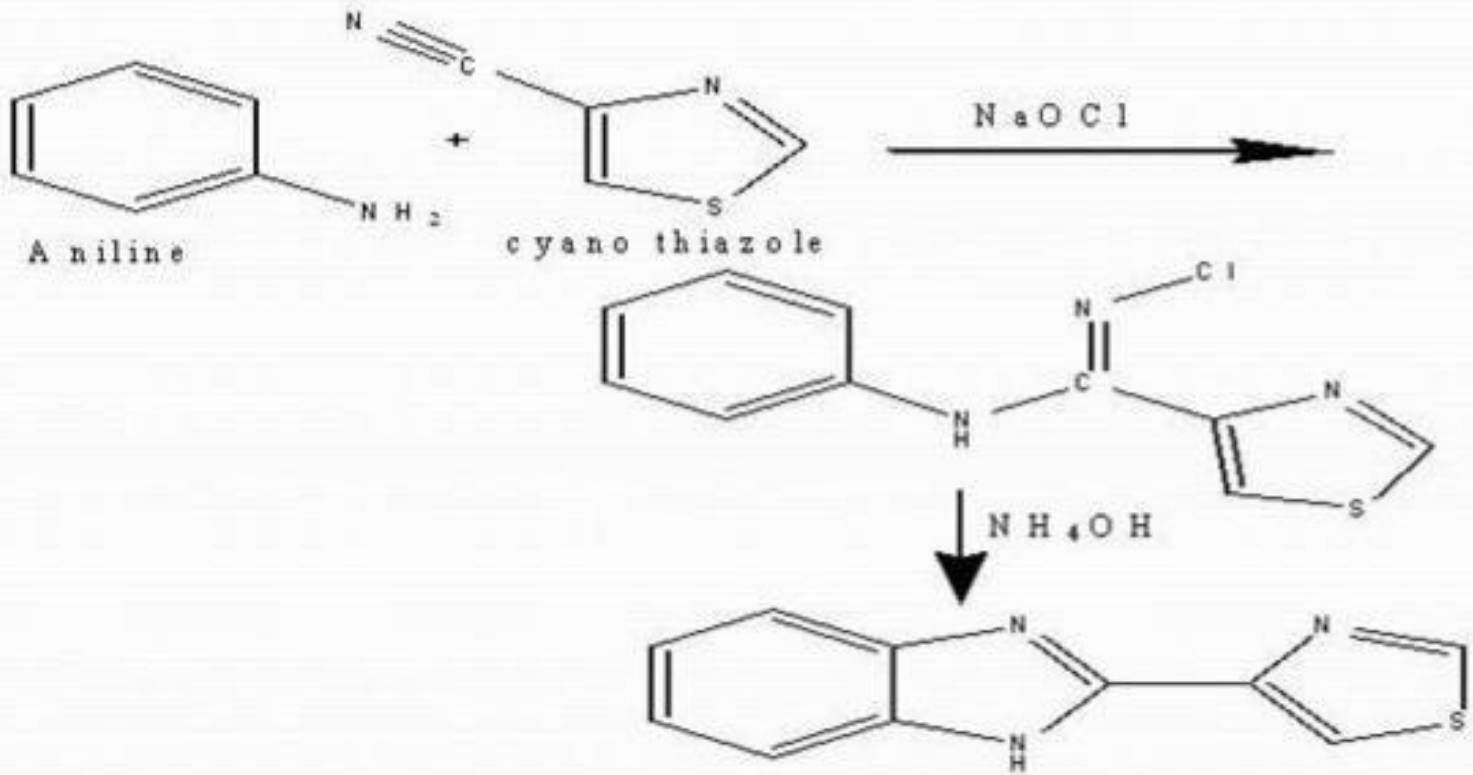
- Mintezol
- 2[4-thiazolyl]benzimidazole



THIABENDAZOLE (cont)

- It has a broad spectrum anthelmintic activity.
- Used to treat
- Enterobiasis (thread worm)
- Ascariasis (round worm)
- Trichuriasis (whip worm)
- In addition to its use in human medicine, it is widely employed in vertinary practice to control helminths.

SYNTHESIS

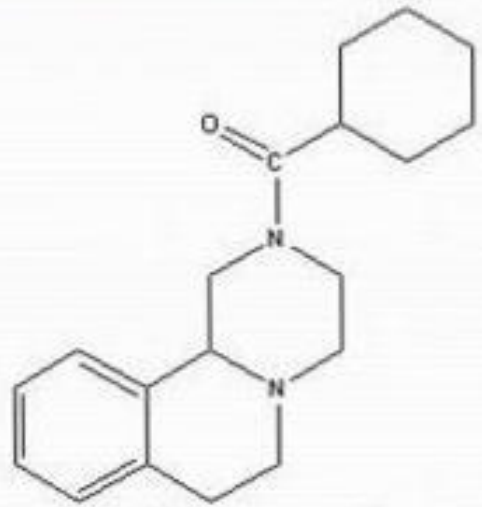

N
C
N
S
NH2
Aniline
cyano thiazole
NaOCl
Cl
N
C
N
H
N
S
NH4OH
N
N
H
N
S

MECHANISM OF ACTION

- bind with β-tubulin and inhibit microtubule polymerization.
- β-tubulin is the precursor of formation of microtubules. Thereby arrest in cell division in nematodes.
- **Biochemical Changes**
- Inhibition of mitochondrial fumerate reductase
- Reduced glucose transport
- Uncoupling of oxidative phosphorylation

PRAZIQUANTEL

- Biltricide

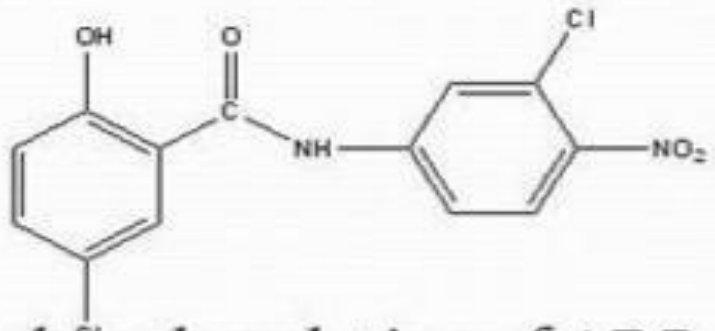


- 2-(cyclohexyl carbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one.
- It increases cell membrane permeability of susceptible worms, resulting in loss of intracellular calcium and loss of extracellular sodium.

- Massive contractions & ultimate paralysis of the fluke musculature occurs.
- The worms lose grip of intestinal mucosa and are expelled.
- USE- It has become the agent of choice for the treatment of infections caused by fluke infections

NICLOSAMIDE

- Cestocide, Mansonil, Yomesan
- 5-chloro-N-(2-chloro -4 nitrophenyl)-2-hydroxy benzamide



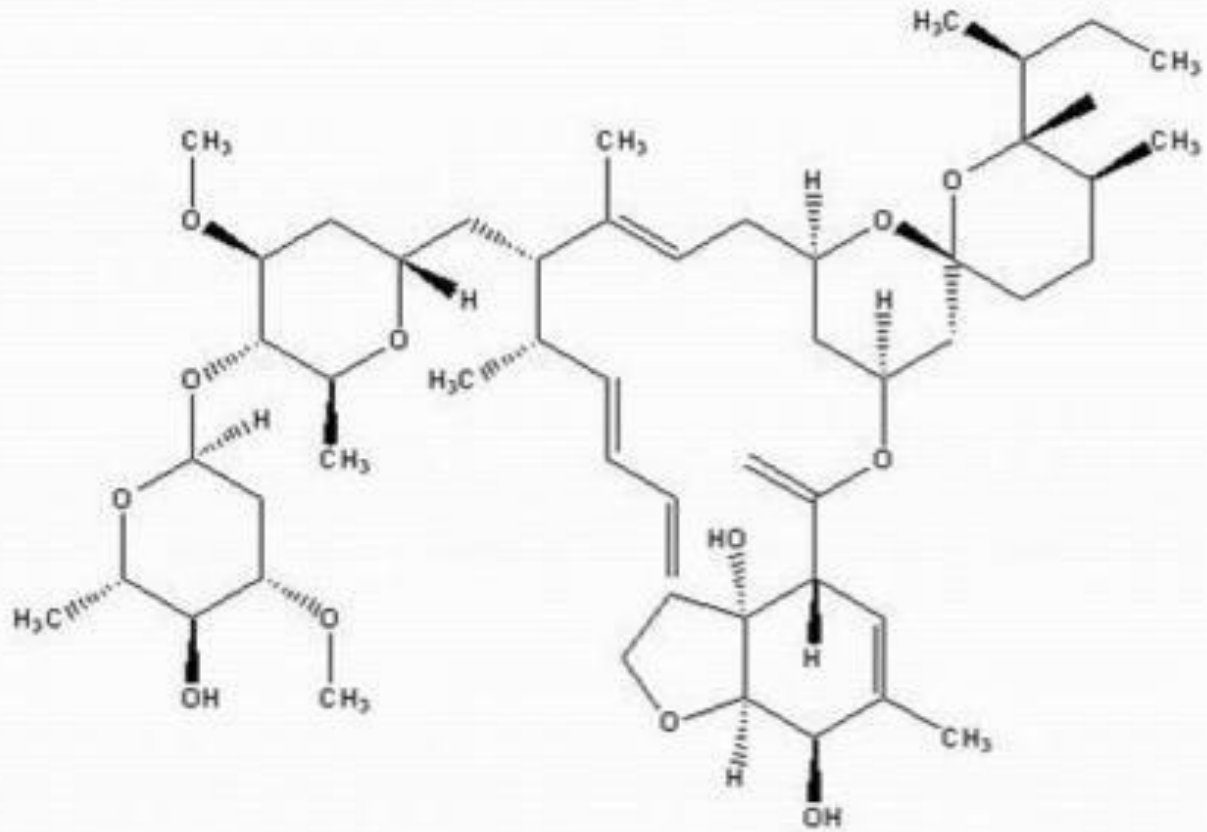
- MOA: The drug inhibits anerobic phosphorylation of ADP by the mitochondria of the parasite, and interfering with anerobic generation of ATP by the Tape worm.
- So it inhibits seperation and blocking glucose absorption by the intestinal nematode function.

- SAR- For the activity, the OH group of benzoic acid moiety had to be in 2 nd position.
- Uses- Agent for choice for the treatment of Taenia solium and Taenia saginata.
- A saline purge 1-2 hr after the ingestion of this drug is recommended to remove the damaged scolex & worm infections.
- Quinacrine can aid for this purpose.

Ivermectin

- Is the drug of choice for the treatment of onchocerciasis (river blindness) caused by *Onchocerca volvulus* and for cutaneous larva migrans and strongyloidiasis.
- *Ivermectin* targets the parasite's glutamate-gated chloride channel receptors. Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis of the worm.
- Dose: 10-15 mg oral dose with 400 mg of albendazole. Given annually for 5-6 years for filariasis.

IVERMECTIN



- Massive contractions & ultimate paralysis of the fluke musculature occurs.
- The worms lose grip of intestinal mucosa and are expelled.
- USE- It has become the agent of choice for the treatment of infections caused by fluke infections