

“ANTHEMINTICS”

Presented By

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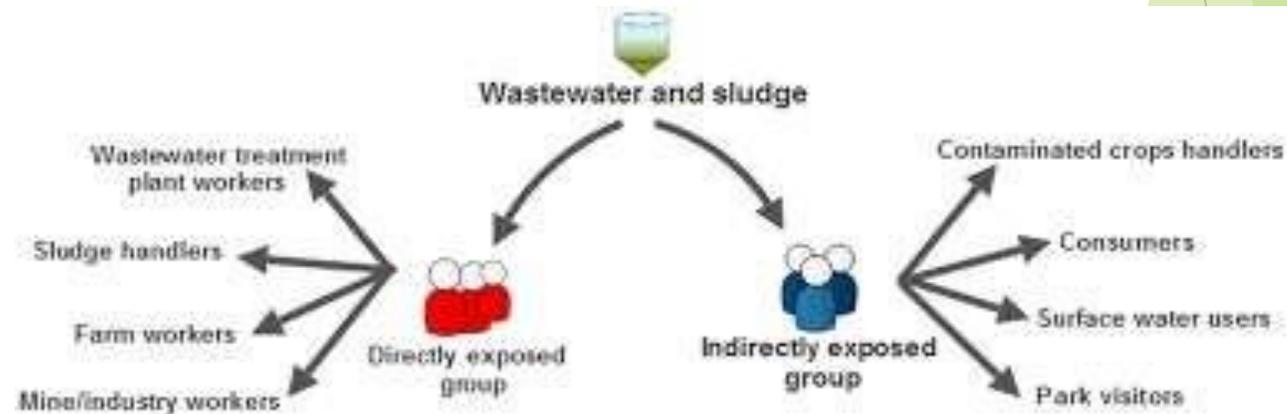
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INTRODUCTION

- ▶ Helminth means worms.
- ▶ Helminthiasis is an infections caused by parasitic worms.
- ▶ Anthelmintics are drugs used to treat parasitic infections due to worms.

Anthelmintics act through two mechanism

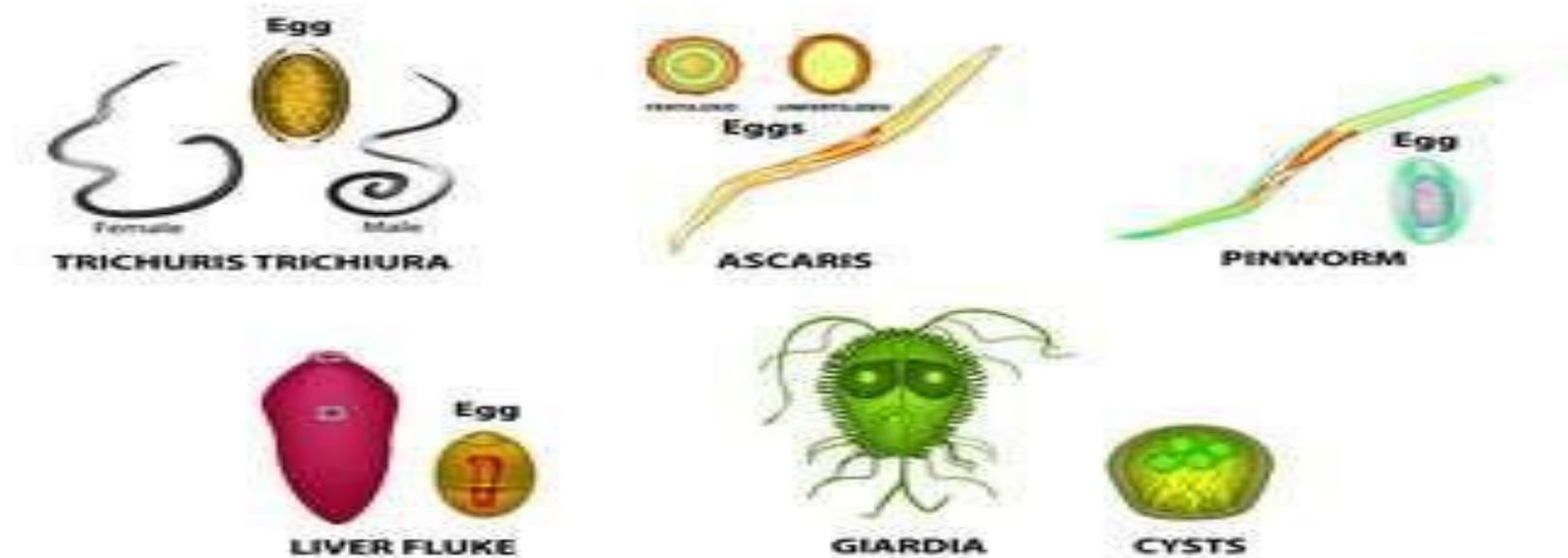
- Vermicide (**kill**) used to kill parasitic intestinal worms.
- Vermifuge (**expel**) used to destroy or expel worms in the intestine.



Helminths are 3 types

- ▶ Nematodes (round worms) - ascarids (Ascaris), filarias, hookworms, pinworms (Enterobius), and whipworms (Trichuris trichiura)
- ▶ Cestodes (tape worms) - multiple species of flat worms, Taenia saginatum, Taenia solium(cysticercosis, hydatid(echinococcus),
- ▶ Trematodes (flukes) - liver flukes, lung flukes, schistosoma

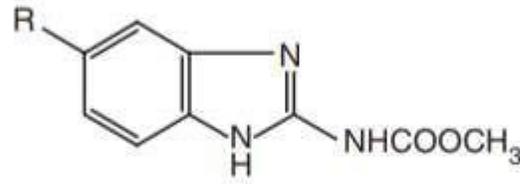
SET OF HELMINTHS



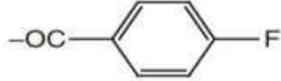
BASED ON CHEMICAL STRUCTURES

- ▶ Benzimidazoles : Albendazole , Mebendazole , Flubendazole, Cyclobendazole
Thiabendazole, Fenbendazole, Oxibendazole, Parbendazole
- ▶ Quinolines and isoquinolines [Heterocyclics]: Oxamniquine, Praziquantel
- ▶ Piperazine derivatives: Piperazine citrate, Diethyl carbamazepine
- ▶ Vinyl pyrimidines: Pyrantel pamoate, Oxantel
- ▶ Amides : Niclosamide
- ▶ Natural products: Ivermectin
- ▶ Organo phosphorus: Metrifonate
- ▶ Imidazothiazoles: Levamisole
- ▶ Nitro derivatives: Niridazole

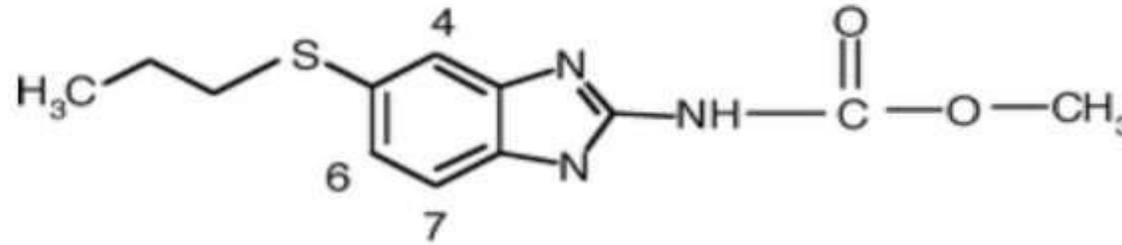
BENZIMIDAZOLES



- ▶ **Benzimidazole** is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of **benzene and imidazole**.
- ▶ Many anthelmintic drugs (albendazole, mebendazole, etc.) belong to the benzimidazole class of compounds.

Drug	R
Albendazole	—S—CH ₂ CH ₂ CH ₃
Mebendazole	—COC ₆ H ₅
Flubendazole	—OC—  —F
Cyclobendazole	—OC— 
Dribendazole	—SCH ₂ — 
Fenbendazole	—S—C ₆ H ₅
Oxibendazole	—OCH ₂ CH ₂ CH ₃
Parbendazole	—CH ₂ CH ₂ CH ₂ CH ₃

ALBENDAZOLE



It selectively binds to nematode β -tubulin **inhibiting polymerization**, thus preventing the formation of microtubules and so stopping cell division. Impaired uptake of glucose, leading to depletion of glycogen, and reduced stores of ATP has also been noted.

SAR

- ▶ Variation in the position of C 5 results in very active compound with low toxicity.
- ▶ Replacement of NHCOCH₃ by aromatic ring prevents the metabolic inactivation.

USES

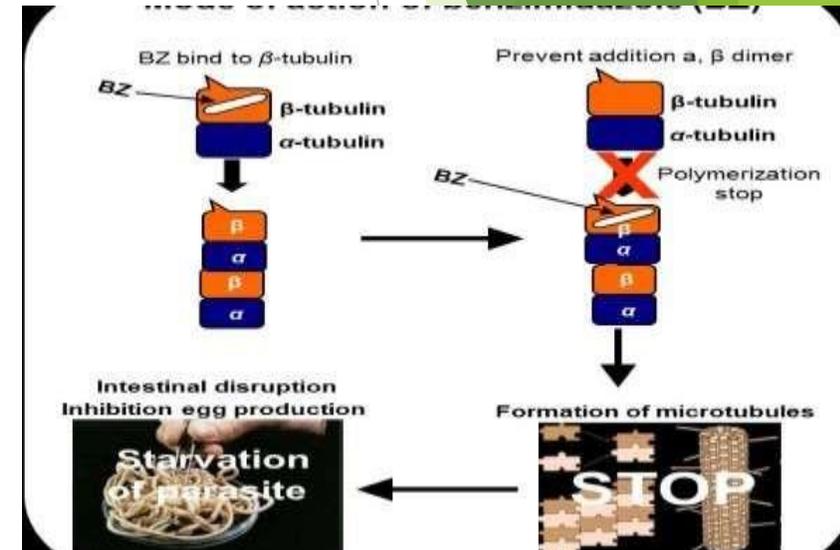
- ▶ treatment of roundworm, pinworm, hookworm infection
- ▶ alternative treatment of threadworm, filariasis
- ▶ hydatid disease & cysticercosis

ADR

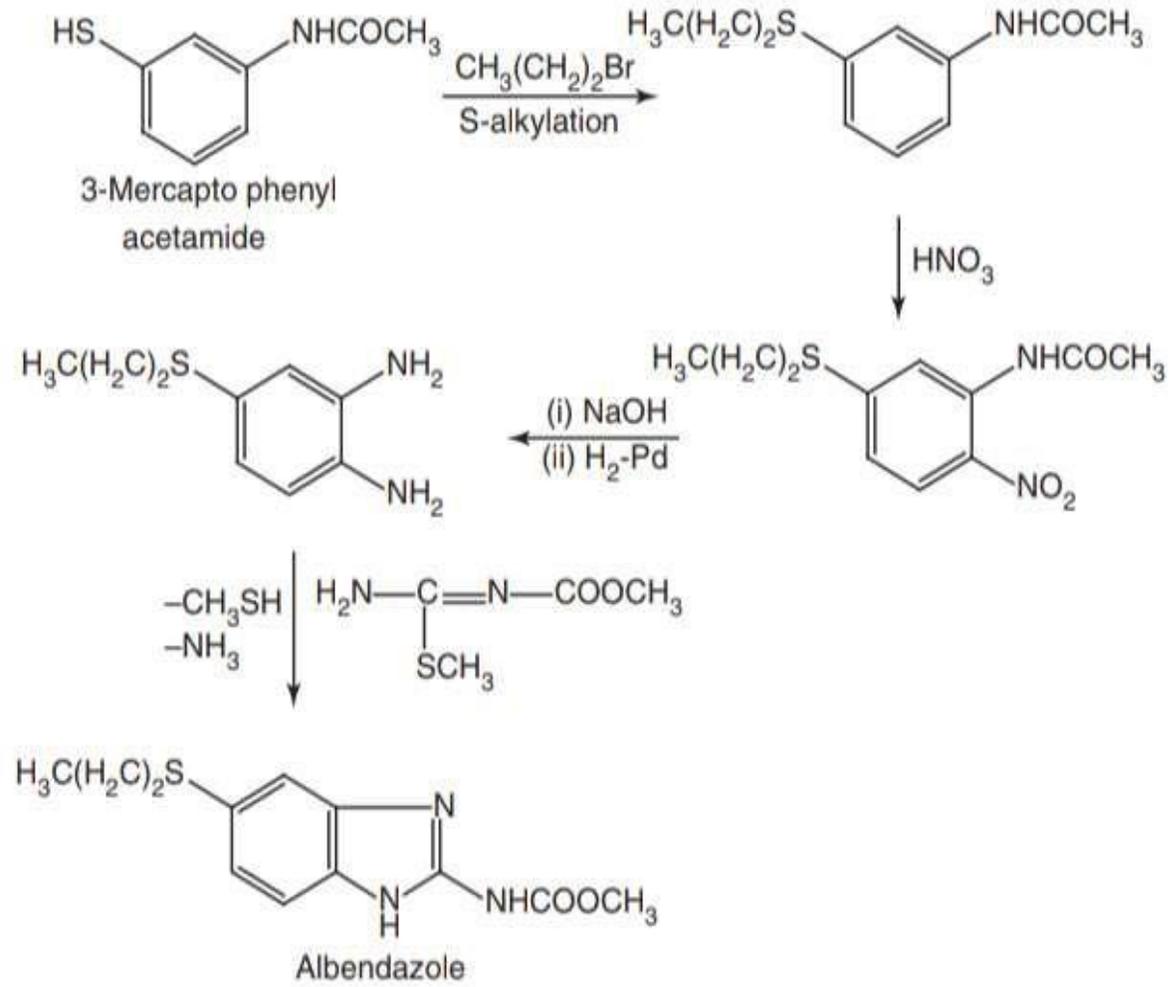
- ▶ Well tolerated; gastrointestinal side effects are known, prolonged use as in hydatid or in neurocysticercosis causes headache, alopecia, jaundice, neutropenia.

DOSE:

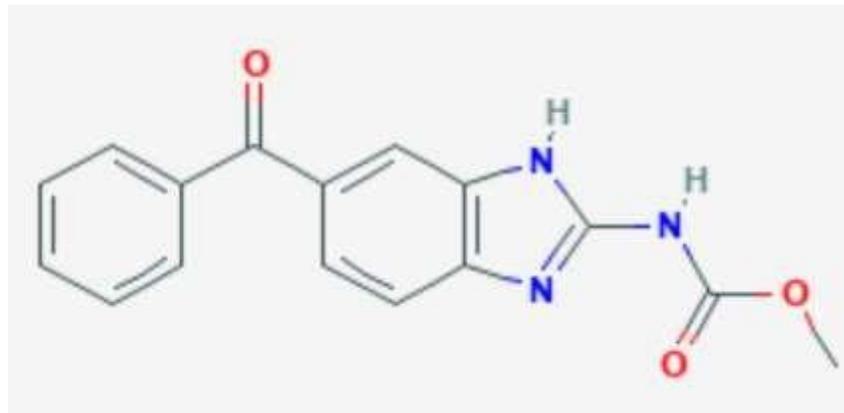
400mg/kg adult dose



Synthesis

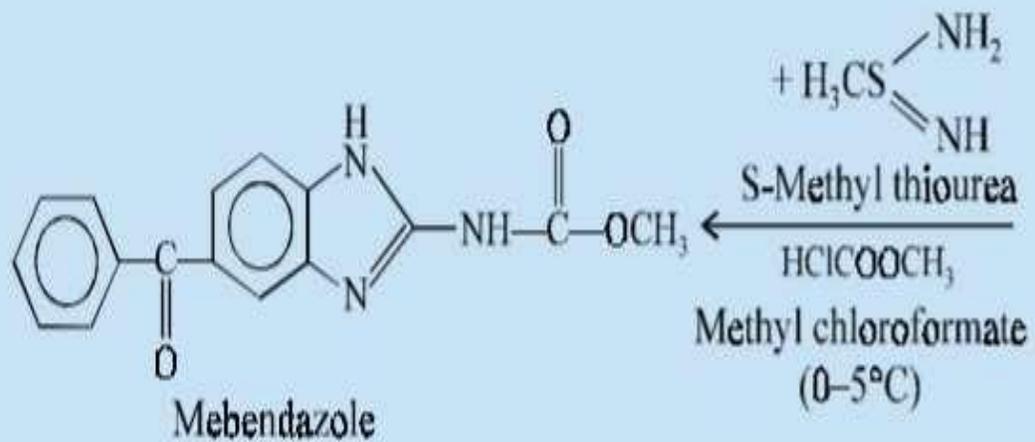
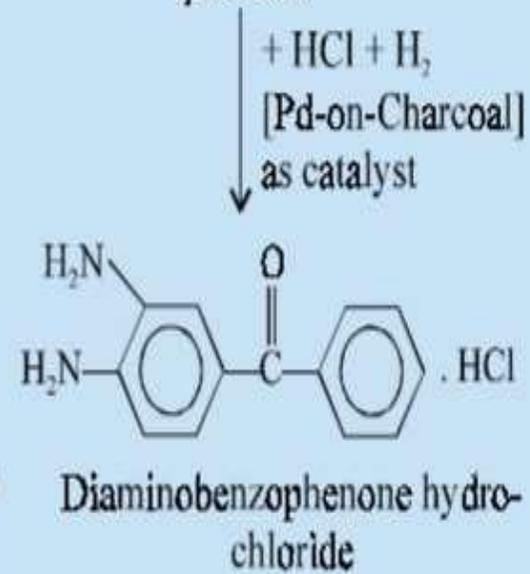
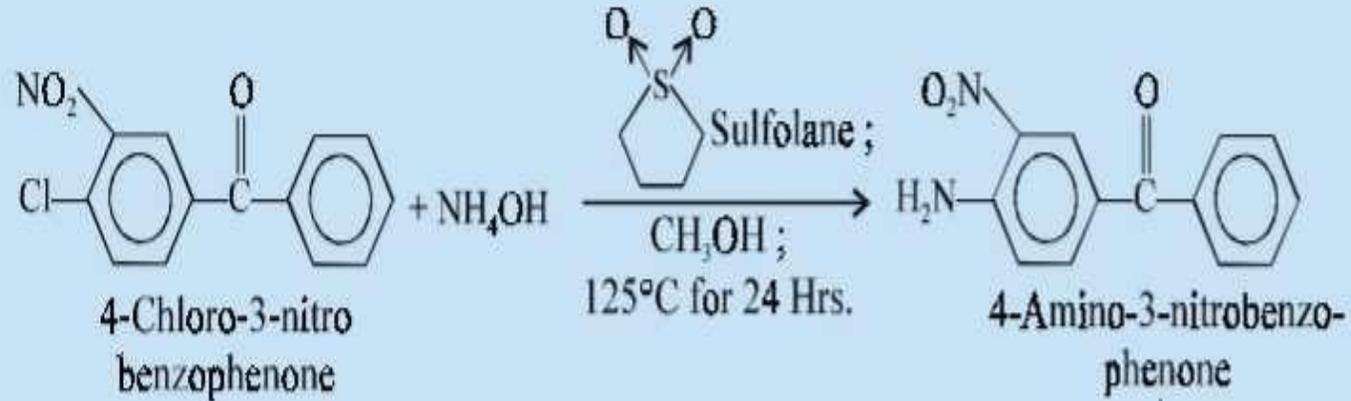


MEBENDAZOLE

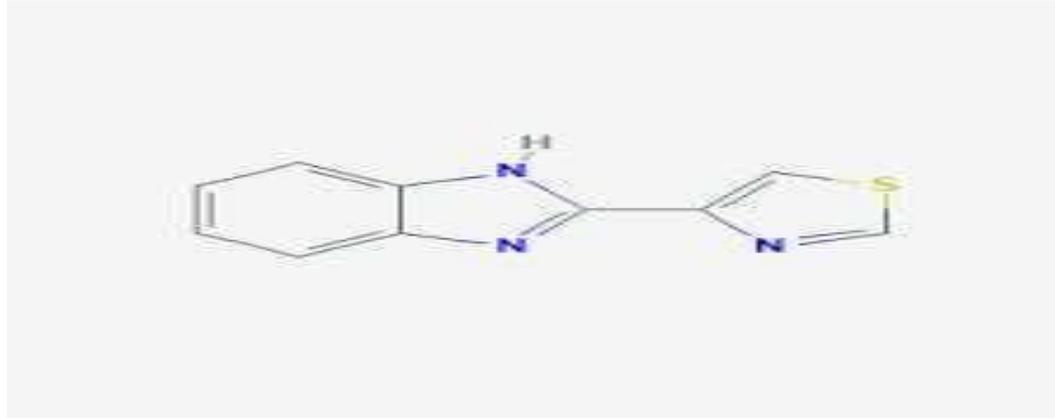


- ▶ Mebendazole is a synthetic benzimidazole that has a wide spectrum of anthelmintic activity and a low incidence of adverse effects
- ▶ **USES:**
treatment of infections by whipworm eggs, pinworm, hookworms, and roundworm.
- ▶ **MOA:**
It acts by inhibiting microtubule synthesis. Its bind with parasite 'β-tubulin' and inhibit its polymerization. It blocks glucose uptake in parasite and depletes its glycogen stores.
- ▶ **ADS:**
Well tolerated, mild nausea, vomiting, diarrhea, and abdominal pain have been reported infrequently. hypersensitivity reactions (rash, urticarial)
- ▶ **DOSE:** 100 mg chewable tablet, 100 mg/5ml suspension

Synthesis



THIABENDAZOLE



MOA: Inhibit glucose uptake and microtubule synthesis in nematodes.

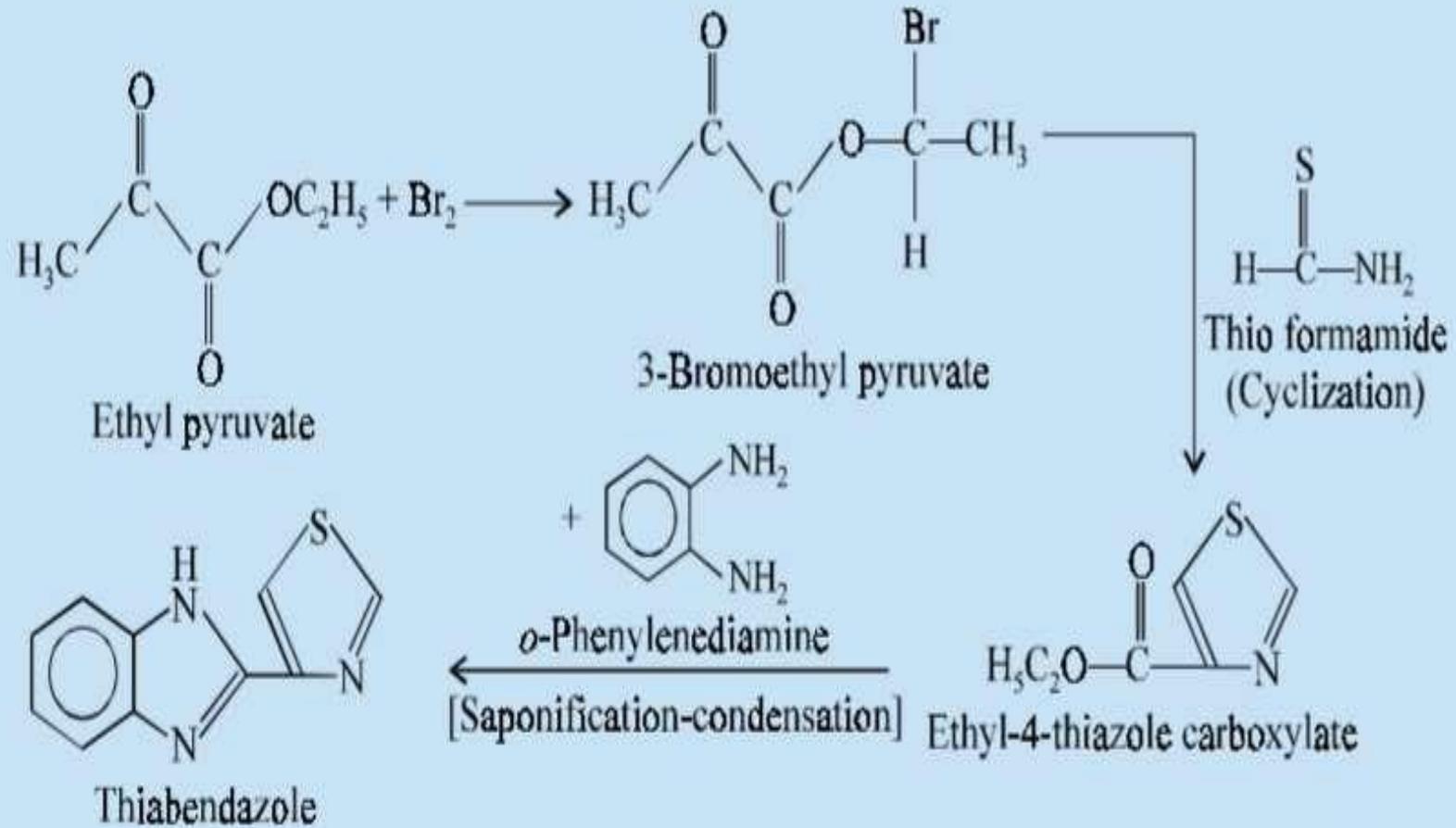
SAR:

- ▶ Replacement of the 4- thiazolyl ring system by a methyl carbamate grouping gave interesting group of anti-helminthes.
- ▶ Substitution at 5th position were introduced to prevent metabolic inactivation.

USES: Primary drug in roundworm and pinworm infection

ADR: GIT upsets, alopecia and agranulocytosis in high dose

Synthesis



QUINOLINE AND ISOQUINOLINE

OXAMNIQUINE

An anthelmintic with schistosomicidal activity against *Schistosoma mansoni*.

MOA:

Oxamniquine is a semisynthetic tetrahydroquinoline and possibly acts by DNA binding, resulting in contraction and paralysis of the worms and eventual detachment from terminal venules in the mesentery, and death. It acts mainly on male worms, but also induces small changes on a small proportion of females.

SAR:

The most critical and Vital entity present in this drug is the presence of 6 - hydroxymethyl moiety;

And the subsequent metabolic activation of the precursor 6- methyl derivatives is equally critical in nature.

DOSES: The dose for oral route after meals depends upon geographical areas. In the western hemisphere, the dose is 15 mg/kg as a single dose, in Africa 15-60 mg/kg over 1-3 days.

PRAZIQUANTEL

An anthelmintic used in most schistosome and many cestode infestations but not nematodes

MOA:

Praziquantel works by causing severe spasms and paralysis of the worms' muscles. This paralysis is accompanied - and probably caused - by a **rapid Ca²⁺ influx** inside the schistosome.

The worms are then either completely destroyed in the intestine or passed in the stool.

USES:

tapeworm infestations

neurocysticercosis

schistosomes

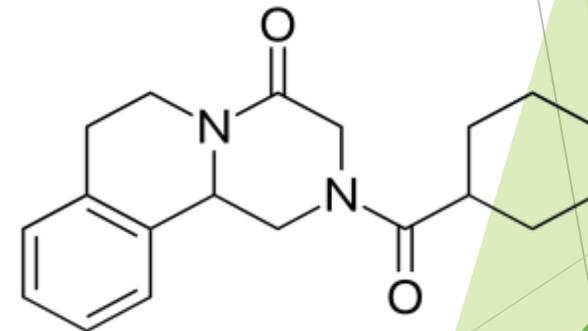
all flukes except liver fluke.

DOSE:

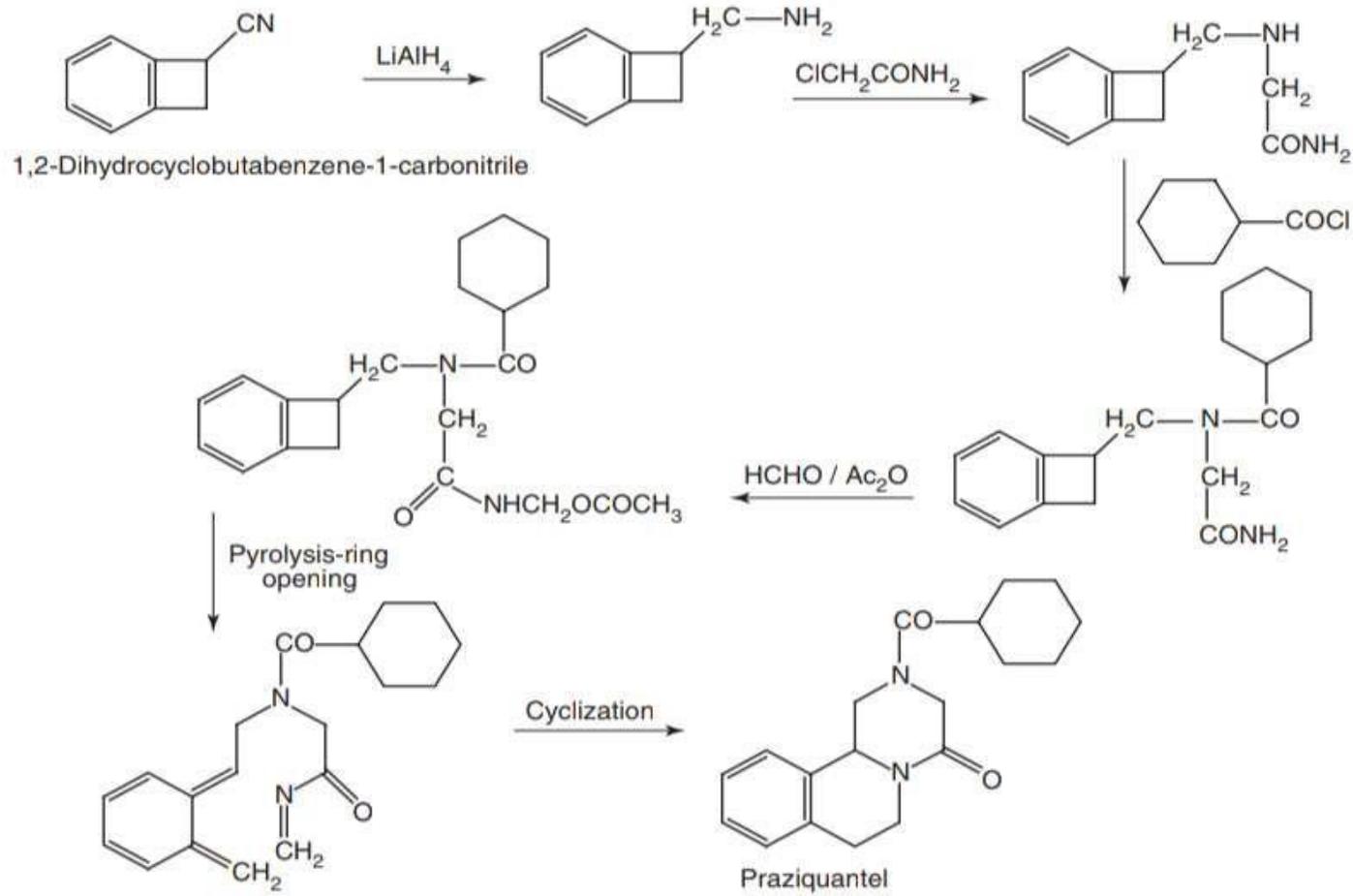
The oral dose is 600mg tablet two to three times in a day.

ADR: Bitter taste, nausea, abdominal pain

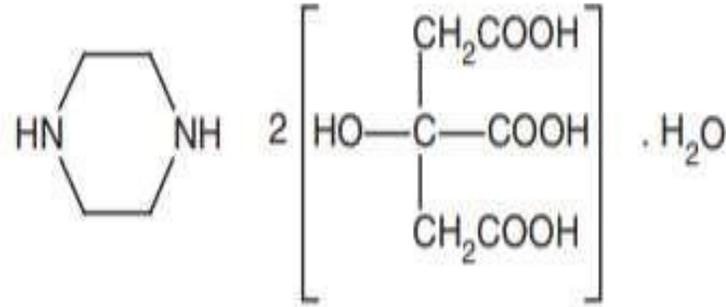
Headache, dizziness and sedation.



Synthesis



PIPERAZINE DERIVATIVES



PIPERAZINE CITRATE

MOA:

Piperazine is a GABA receptor agonist binds selectively to receptors, causing hyperpolarization of ascariasis muscles, resulting in **flaccid paralysis of the worm**, then it is dislodged from the intestinal lumen.

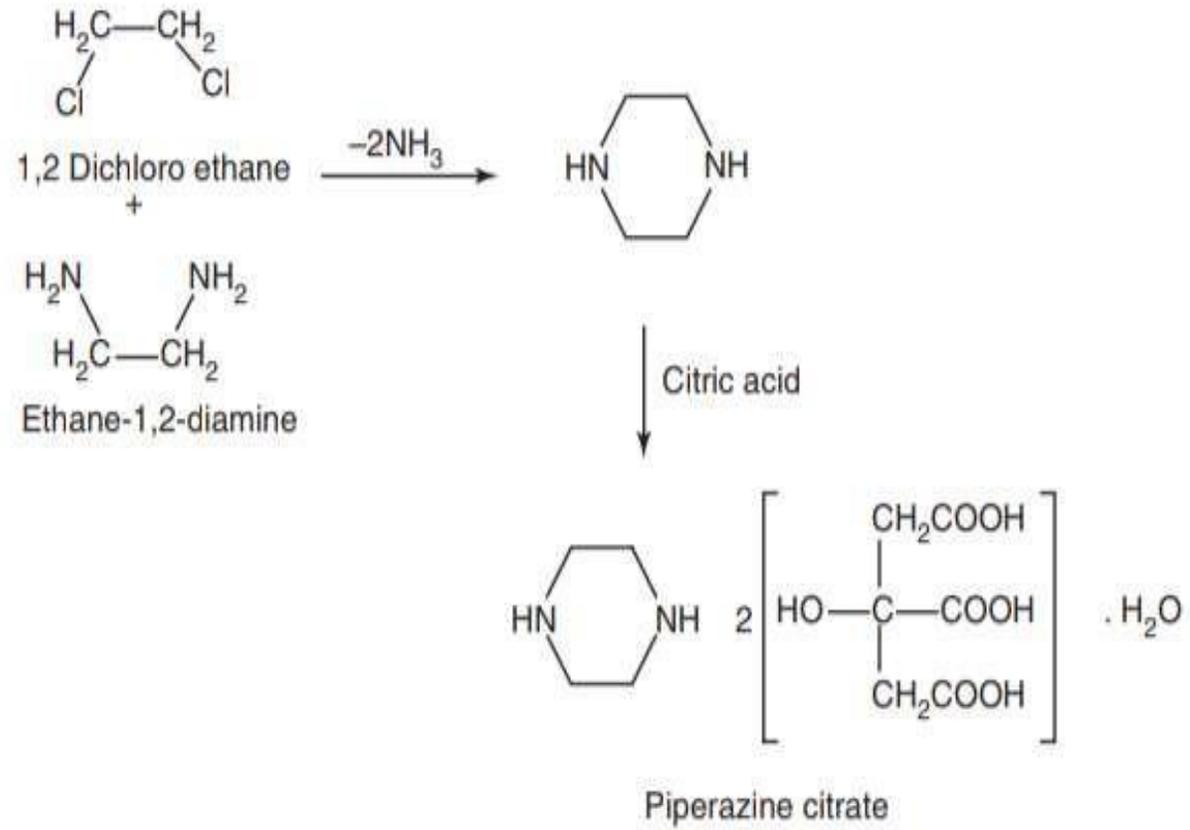
DOSE: The administered dose always orally in the case of ascariasis is 3.5 g as single dose daily for two consecutive days. For oxyuriasis (thread worms) the dose is 2.5 g given for 7 days

USES:

common roundworms (ascariasis) and pinworms (enterobiasis; oxyuriasis).

ADR: nausea, vomiting, abdominal pain, headache neurotoxicity and allergic reactions are rare.

Synthesis



DIETHYL CARBAMAZINE

An anthelmintic used primarily as the citrate in the **treatment of filariasis**

MOA:

Microfilaricidal, death of microfilaria by blocking cyclooxygenase pathway in parasites. It alters the microfilarial membranes so that they are readily phagocytosed by the tissue bound monocytes.

USES:

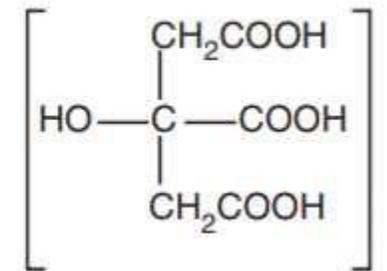
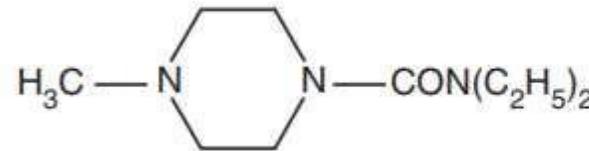
Filariasis, topical eosinophilia

DOSE:

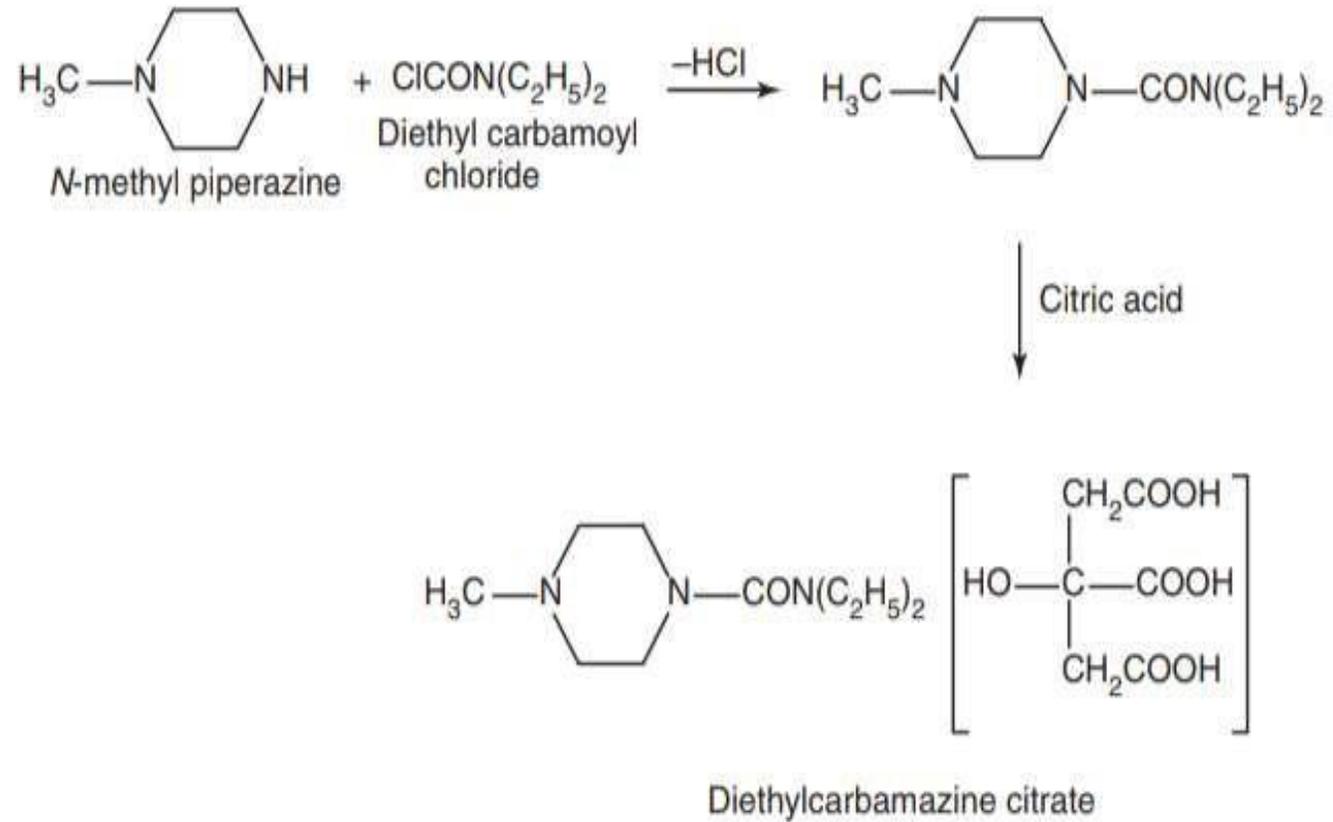
The usual dose is 2 to 3 mg/kg for filariasis

The usual dose is 6 mg per kg. This is taken for four to seven days [eosinophilia]

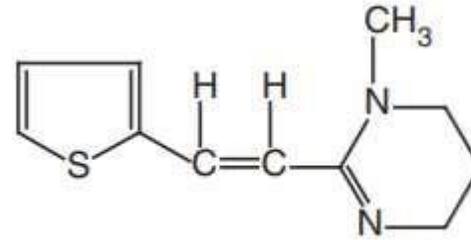
ADR: nausea, vomiting, lethargy, febrile reaction.



Synthesis



VINYL PYRIMIDINES



1-Methyl-2-(2-(thiophen-2-yl)vinyl)-1,4,5,6-tetrahydropyrimidine

PYRANTEL PALMOATE

Originally for thread worm but extended to hook worm and round worms

MOA: Pyrantel is a depolarizing **neuromuscular blocking agent**. It induces marked persistent activation of the nicotinic receptors, which result in spastic paralysis of the worm.

DOSES: The dose for oral suspension or liquid is 50 mg/ml. A single dose of 11 mg/kg for ascariasis and enterobiasis.

USES:

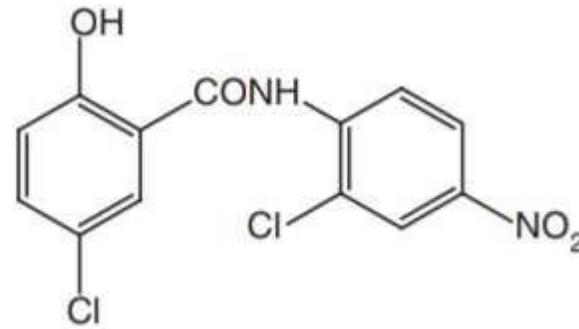
It is an alternative to mebendazole in the treatment of ascariasis and enterobiasis.

ADR:

Nausea , vomiting , diarrhea , stomach / abdominal cramps

Headache ,dizziness , loss of appetite

AMIDES



NICLOSAMIDE

Niclosamide is an anthelmintic which is active against most tapeworms. Highly effective against cestodes infecting man.

- ❖ **MOA:** It acts by **inhibiting oxidative phosphorylation** in mitochondria and interfering with anerobic generation of ATP in tapeworm resulting in energy depletion.
- ❖ **DOSE:**
2 gm as a single dose after a light breakfast.
- ❖ **ADR:** Tastless and nonirritant, minimal absorption from GIT so minimal systemic toxicity.

NATURAL PRODUCTS

IVERMECTIN

- ▶ Ivermectin is an avermectin analogue. It is a broad spectrum anti-parasite medication. Anthelmintics
- ▶ Ivermectin is used for the treatment of certain parasitic roundworm infections.
- ▶ Currently investigated for COVID-19 Treatment

ADR: Mild side effects; Nausea, abdominal pain, constipation, pruritus, lethargy and transient ECG changes

DOSE: A single 10-15 mg oral dose of ivermectin with 400 mg albendazole given annually for 5-6 years has been used for filariasis

MECHANISM OF ACTION:



Ivermectin

↓ Targets

GABA receptors of parasite



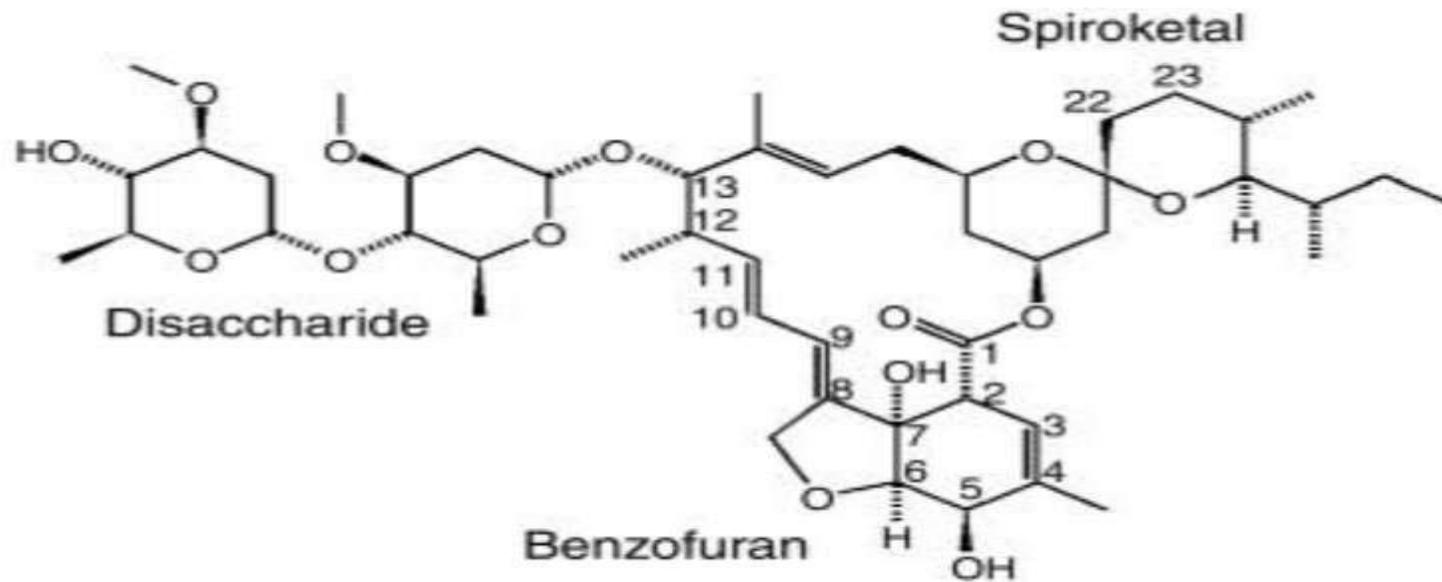
Chloride ion influx enhanced



Hyper polarization occurs

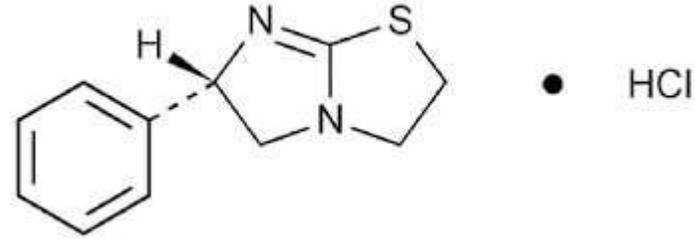


Paralysis of the worm



- ▶ **Structure Activity Relationship**
- ▶ 4-O-substituted derivatives retains biological activity.
- ▶ 5-O-substituted analogue has no biological activity.
- ▶ Presence of hydroxy or methoxy group at 5-position is essential for antiparasitic activity.
- ▶ The presence of two sugar moieties at position 13 is essential for biological activity.
- ▶ Reduction of the 22,23 position of avermectines shows better safety index
- ▶ Aliphatic nature of the ring having 5-OH/OMe is necessary for antiparasitic activity. If the ring is replaced by aromatic ring, then there is no activity.

IMIDAZOTHIAZOLES



LEVAMISOLE

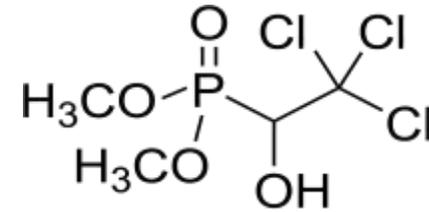
- ▶ They are active against large number of nematodes but their use is restricted to only ascariasis and ancylostomiasis because of poor action against other worms.
- ▶ **MOA:** They stimulate ganglia in worms and cause tonic paralysis which results in **expulsion of live worms**. They also interfere with carbohydrate metabolism (inh. Fumarate reductase)
- ▶ **ADRS:** Nausea, abdominal pain, fatigue, drowsiness or insomnia is low.
- ▶ **DOSE:** The administered dose is 15mg as a single dose, repeated after 1 month to prevent recurrence.

METRIFONATE [ORGANOPHOSPHOROUS COMPOUNDS]

Anthelmintic dose is 7.5mg/kg given orally three times at intervals of 2 weeks.

Irreversible organophosphate acetylcholinesterase inhibitor.

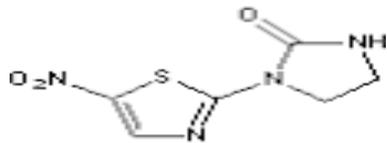
It is a prodrug which is activated non-enzymatically into the active agent dichlorvos. It is used as an insecticide.

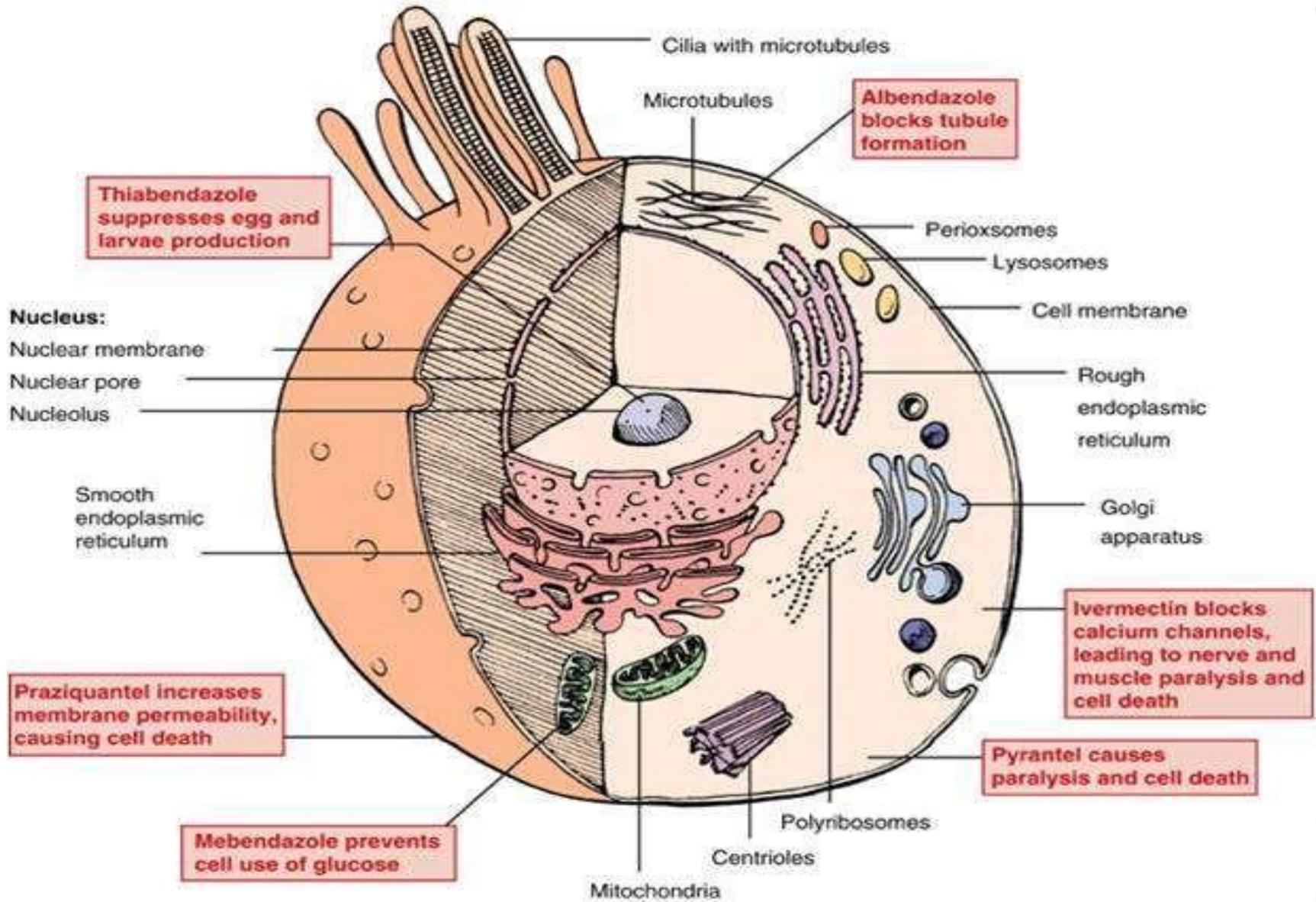


NIRIDAZOLE [NITRO DERIVATIVES]

Used as an anthelmintic agent.

The recommended daily dose by oral route is 25mg/kg daily in two divided doses.





REFERENCE

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- ▶ Textbook of Medicinal chemistry, volume II by V.Alagarsamy
- ▶ Essentials of Medical Pharmacology, K.D Tripathi
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