Chapter 14: Anthelmintics

Anthelmintics: Diethylcarbamazine citrate*, Thiabendazole, Mebendazole*, Albendazole, Niclosamide, Oxamniquine, Praziquantal, Ivermectin.

14.1. ANTHELMINTICS

- Anthelmintics are drugs used to treat parasitic infections due to worms.
- Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths
- Worms that are pathogenic to human beings, namely, **metazoa** are conventionally classified into **round worms** (nematodes) and two types of **flatworms**, that is, flukes (trematodes) and tapeworms (cestodes).
- Anthelmintics act locally either to expel the worms from the gastrointestinal tract or systemically to eradicate the species and the developing forms of helmintics that invade the organs and tissues

Drugs Classification

I. Benzimidazoles

- These are effective against GI nematodes. These are highly effective against *ascaris, enterobius, trichuris,* and hookworm infections as single or mixed infections.

Drugs: Mebendazole*, Albendazole, Thiabendazole, Flubendazole, Cyclobendazole, Oxibendazole

II. Quinolines and isoquinolines: Oxamniquine, Praziquantal

III. Piperazine derivatives: Piperazine citrate, Diethyl carbmazine

IV. Vinyl pyrimidines: Pyrantel pamoate, Oxantel

V. Amides: Niclosamide

VI. Natural products: Ivermectins

VII. Organo phosphorus: Metrifonate

VIII. Imidazothiazoles: Levamisole

IX. Nitro derivatives: Niridazole

TABLE 61.1 Choice of drugs for helminthiasis

	Worm	First choice drugs	Alternative drugs
1.	**ROUNDWORM** *Ascaris lumbricoides*	Mebendazole, Albendazole, Pyrantel	Piperazine, Levamisole Ivermectin
2.	**HOOKWORM**		
	Ancylostoma duodenale	Pyrantel, Mebendazole, Albendazole	Levamisole
	Necator americanus	Mebendazole, Albendazole	Pyrantel
3.	**PIN WORM** *Enterobius (Oxyuris) vermicularis*	Pyrantel, Mebendazole, Albendazole	Piperazine
4.	**THREAD WORM** *Strongyloides stercoralis*	Ivermectin	Albendazole
5.	**WHIPWORM** *Trichuris trichiura*	Mebendazole	Albendazole
6.	*Trichinella spiralis*	Albendazole	Mebendazole
7.	**FILARIA** *Wuchereria bancrofti, Brugia malayi*	Diethyl carbamazine, Ivermectin	Albendazole
8.	**GUINEAWORM** *Dracunculus medinensis*	Metronidazole	Mebendazole
9.	**TAPEWORMS**		
	Taenia saginata	Praziquantel, Niclosamide	Albendazole
	Taenia solium	Praziquantel	Niclosamide, Albendazole
	Hymenolepis nana	Praziquantel	Niclosamide, Nitazoxanide
	Neurocysticercosis	Albendazole	Praziquantel
10.	**HYDATID DISEASE**		
	Echinococcus granulosus, *E. multilocularis*	Albendazole Albendazole	Mebendazole

Sourece: KD Tripathi, Medical Pharmacology

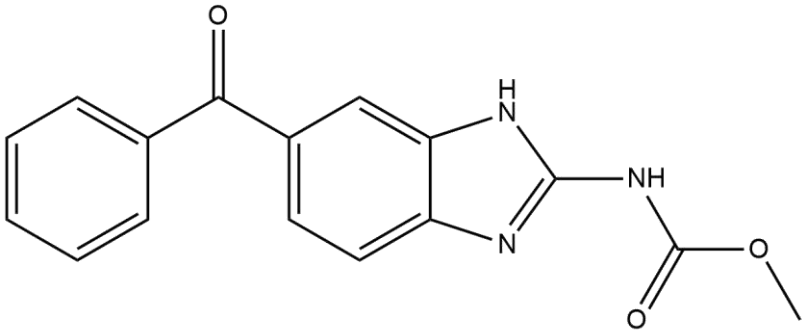
14.2. MEDICINAL CHEMISTRY AND PHARMACOLOGY OF ANTHELMINTICS

I. Benzimidazoles

MOA: Inhibit the cell division

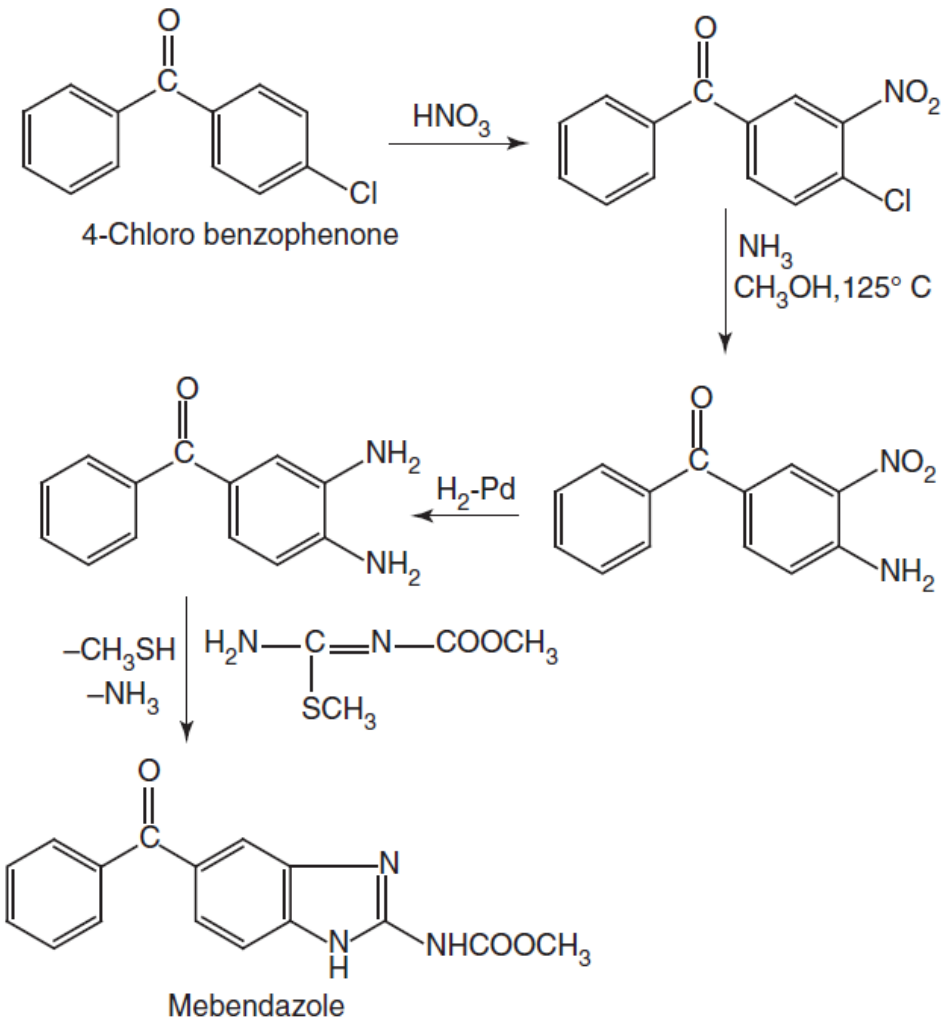
These drugs act by blocking the glucose transportation in the parasites and lead to the depletion of glycogen storage of the intracellular microtubules in the cells of the worms, thereby arresting cell division in the metaphase. The major site of action is microtubular protein β tubilin of the parasite. These drugs are bound with β tubilin and inhibit the polymerization.

A) Mebendazole



methyl (6-benzoyl-1*H*-benzo[*d*]imidazol-2-yl)carbamate

Synthesis

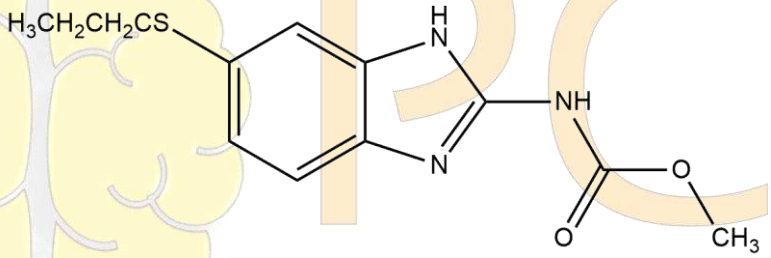


Pharmacology

- It is benzimidazole derivative introduced in 1972.
- The immobilizing and lethal action of mebendazole is slow and takes 2–3 days.
- The site of action of mebendazole appears to be the microtubular protein ‘β-tubulin’ of the parasite as discussed above

- **Pharmacokinetics**: Absorption of mebendazole from intestines is minimal; 75–90% of an oral dose is passed in the faeces. The fraction absorbed is excreted mainly as inactive metabolites in urine/faeces
- **ADR**: well tolerated drugs, having some side effects like diarrhoea, nausea and abdominal pain. Loss of hair and granulocytopenia have been reported with high doses. It is contraindicated in pregnancy as per animal data.
- **Dose**: 100 mg for adult and >2Y
- **Uses**:
    - ✓ 100 mg twice a day for 3 days: Roundworm, Hookworm, Whipworm
    - ✓ 100 mg single dose, repeated after 2-3 week: Pin worm *(Enterobius)*
    - ✓ 200 mg BD for 4 days: Trichinosis.
    - ✓ 200–400 mg BD or TDS for 3–4 weeks: Hydatid disease.

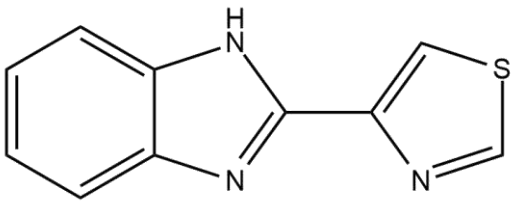
B) Albendazole



methyl (6-(propylthio)-1*H*-benzo[*d*]imidazol-2-yl)carbamate

- It has broad-spectrum activity and excellent tolerability of its predecessor (mebendazole), and has the advantage of single dose administration in many infestations.
- One dose treatment has produced cure rates in ascariasis, hookworm (both species) and enterobiasis which are comparable to 3 day treatment with mebendazole.
- Three-day treatment has been found necessary for tapeworms including *H. nana*.
- It is used in various infective diseases like *Ascaris,* hookworm, *Enterobius* and *Trichuris,* Trichinosis, Neurocysticercosis, Hydatid disease, Filariasis.

C) Thiabendazole

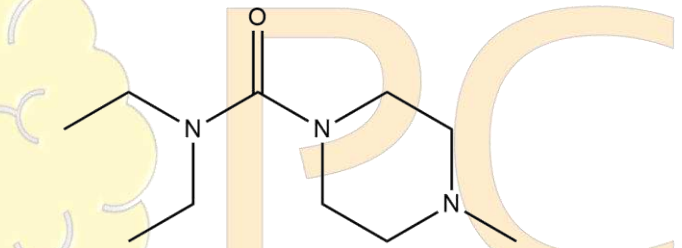


4-(1*H*-benzo[*d*]imidazol-2-yl)thiazole

- This congener of thiabendazole became very popular because it retained the broad-spectrum anthelmintic activity but not the toxicity of its predecessor.
- It was the first benzimidazole polyanthelmintic introduced in 1961, which covered practically all species of nematodes infesting the g.i.t.—roundworm, hookworm, pin worm, *Trichuris, Strongyloides* and *Trichinella spiralis*.
- It also inhibits development of the eggs of worms and kills larvae.
- Thiabendazole affords symptomatic relief in cutaneous larva migrans and skeletal muscle symptoms produced by migration of *Trichinella spiralis* larvae to muscles, because it has anti-inflammatory action as well.
- Symptomatic relief also occurs in guinea worm disease.

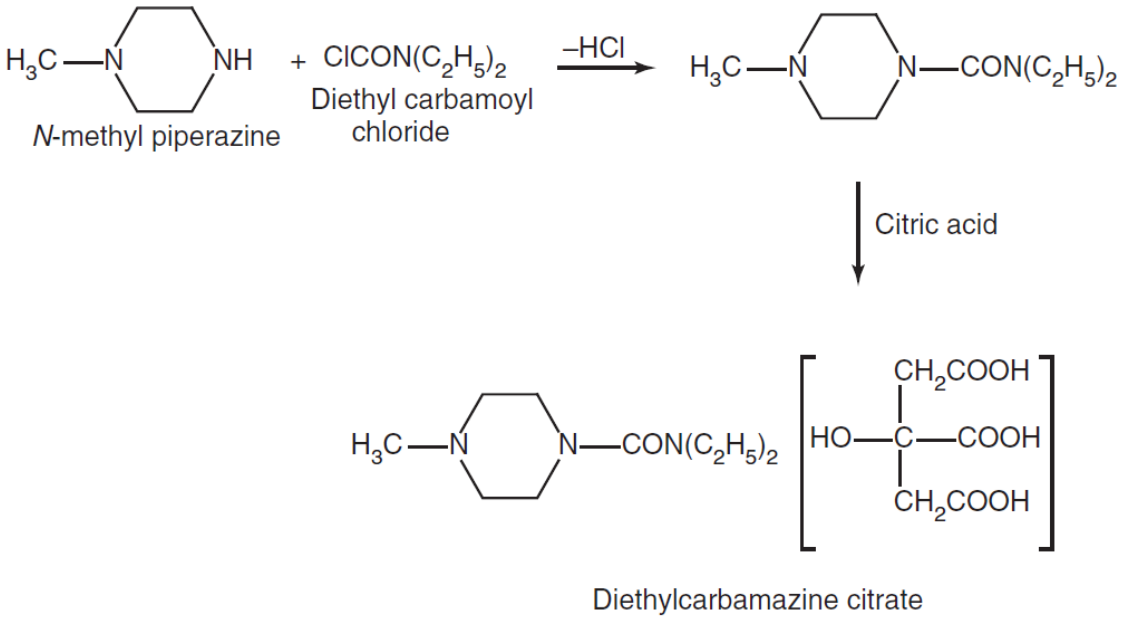
II. Piperazine derivatives

D) Diethylcarbamazine citrate*



N,*N*-diethyl-4-methylpiperazine-1-carboxamide

Synthesis:



N-methyl piperazine

Diethylcarbamazine citrate

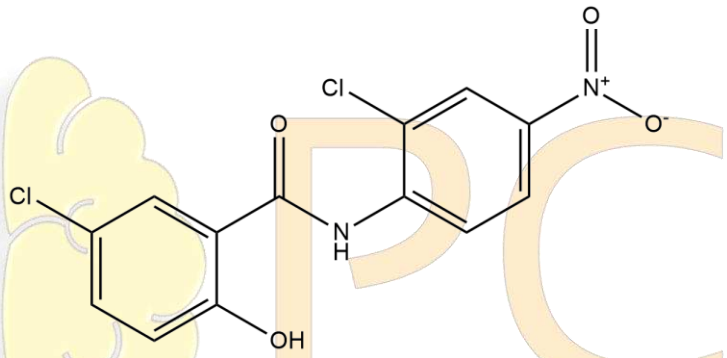
MOA: It involve in the sensitization the microfilariae to phagocytosis. It also involve in inflammatory pathway by interfering with the COX pathways.

Uses:

- ✓ it is the drug of choice for treating filariasis infections (*Wuchereria bancrofti, Brugia malayi, and B. timori)*. In adequate dosage, it clears the blood rapidly of the microfilariae and appears to be curative. Antihistamines or corticosteroids may be needed to control the allergic reaction caused by the disintegration of microfi lariae.
- ✓ Also used in loiasis due to *Loa loa* (but it may cause encephalopathy)

III. Amides

E) Niclosamide



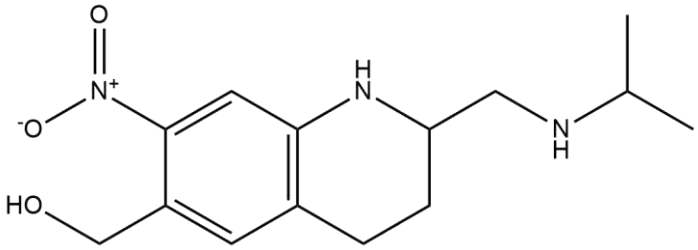
5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

MOA: Niclosamide is also a potent mollusicide, which is effective against *Biomphaloria glabrata*, the principle action of the drug may be to inhibit anaerobic phosphorylation of adenosine diphosphate (ADP) by the mitochondria of the parasite, an energy producing process.

Uses: It is mainly used in tapeworm infection.

IV. Vinyl pyrimidines

F) Oxamniquine

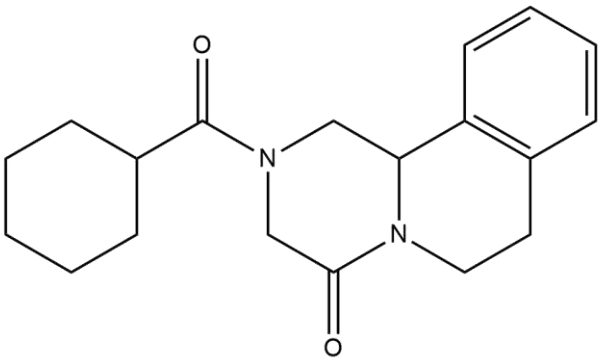


(2-((isopropylamino)methyl)-7-nitro-1,2,3,4-tetrahydroquinolin-6-yl)methanol

MOA: Inhibits the nucleic acid synthesis of the metabolism resulting in contraction and paralysis of the worm and death.

Uses: It is used in treatment of schistosomiasis caused by *Schistosima mansoni*

G) Praziquantal



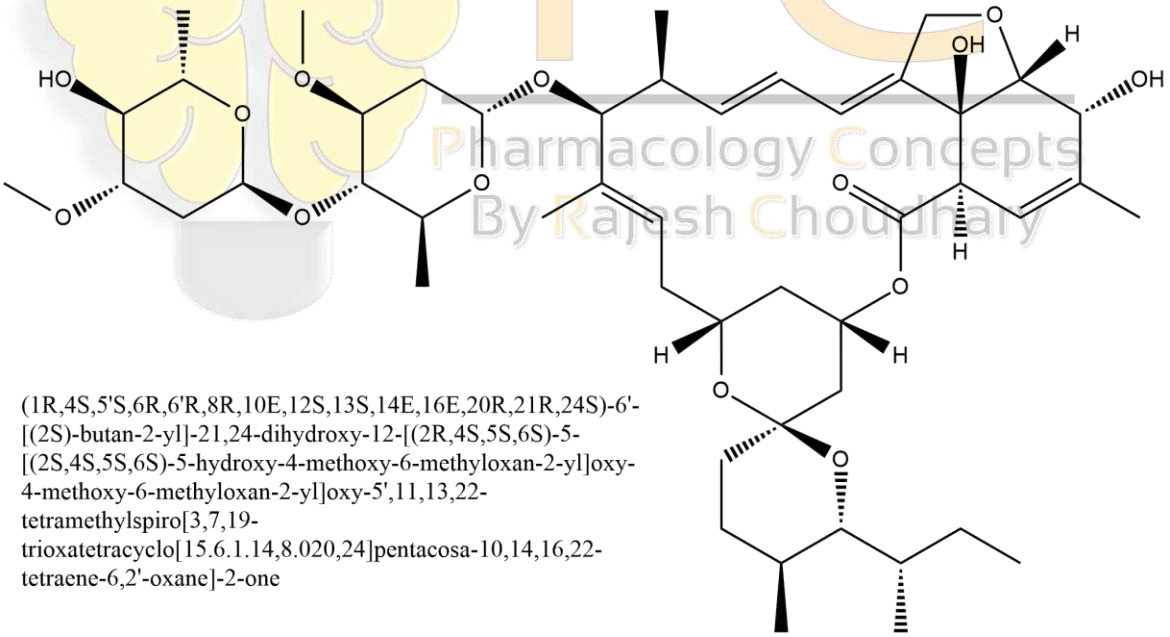
2-(cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1*H*-pyrazino[2,1-*a*]isoquinolin-4(11b*H*)-one

MOA: it causes rapid Ca2+ influx inside the schistosome resulting sever spasm and paralysis of the worm muscle and death.

Uses: Used in variety of parasite worm infections like schistosomiasis, clonorchiasis, opisthorchiasis, tapeworm infection, hydatid disease and other fluke infection.

V. Natural

H) Ivermectin



(1R,4S,5'S,6R,6'R,8R,10E,12S,13S,14E,16E,20R,21R,24S)-6'-[(2S)-butan-2-yl]-21,24-dihydroxy-12-[(2R,4S,5S,6S)-5-[(2S,4S,5S,6S)-5-hydroxy-4-methoxy-6-methyloxan-2-yl]oxy-4-methoxy-6-methyloxan-2-yl]oxy-5',11,13,22-tetramethylspiro[3,7,19-trioxatetracyclo[15.6.1.14,8.020,24]pentacosa-10,14,16,22-tetraene-6,2'-oxane]-2-one

22,23-dihydroavermectin

MOA: Avermectins specifically open the chloride channels in the invertebrate system distinct from the GABA-gated and glutamate-gated chloride channels.

Uses:

- ✓ The drug avermectin is now effectively being used to treat and control *onchocera volvulus*, the filarial infection responsible for liver blindness.
- ✓ Also used in head lice, scabies, river blindness (ochorcerciasis), and lymphatic filariasis.

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