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Antihelmintic Drugs: A Comprehensive Review of Methods of Synthesis and Mechanism

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ABSTRACT

Antihelmintic drugs are essential in the treatment of parasitic worm infestations, which remain a significant public health challenge worldwide. These drugs target various stages of the helminth lifecycle, including larval, adult, and egg stages, helping to reduce the burden of parasitic diseases such as ascariasis, schistosomiasis, and strongyloidiasis. This comprehensive review examines the different classes of antihelmintic agents, focusing on their methods of synthesis and mechanisms of action. The major categories include Benzimidazoles, macrocyclic lactones, imidazothiazoles, and others, each with distinct synthetic routes and modes of action. Benzimidazoles, such as Albendazole and Mebendazole, are synthesized using a combination of condensation and cyclization reactions, targeting microtubule polymerization to disrupt helminth cell division. Macrocyclic lactones, including Ivermectin, are derived from fermentation processes, and they inhibit neuromuscular transmission by binding to glutamate-gated chloride channels. Imidazothiazoles, like levamisole, act on nicotinic acetylcholine receptors, leading to paralysis and expulsion of the parasite. The review also discusses emerging antihelmintic agents, including those derived from natural sources, and the challenges associated with resistance development. Understanding the synthesis, mechanism of action, and potential resistance mechanisms is vital for the continued advancement of antihelmintic therapy. This review provides insights into current trends and future directions for the design of more effective and sustainable antihelmintic drugs.

Keywords: *Antihelmintic drugs, parasitic infections, Benzimidazoles, Macrocyclic lactones, Drug resistance*

1. INTRODUCTION

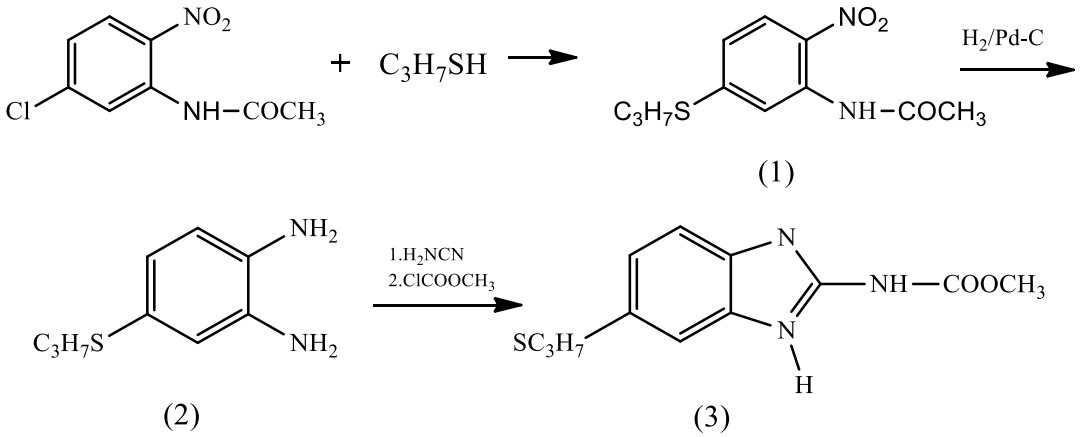
Helminth infections are some of the most common diseases found in both developing and developed countries [1]. Worldwide, it is estimated that around 2 billion people are affected by intestinal nematodes [2].Antihelmintic medications treat helminth infections, but existing drugs are costly and lose effectiveness due to resistance. These infections are closely linked to poverty and are often overlooked until symptoms appear. They are more common in areas with poor sanitation and contaminated water. Effective control relies on antihelmintic chemotherapy, as vaccines are not yet available. Many of the

WHO's neglected tropical diseases, like ascariasis and schistosomiasis, are caused by helminths, and new treatments are sought through empirical and selective methods.[3].Antihelminthic medications are designed to eliminate helminths and rid host organisms of these parasites. Some examples of these drugs include Albendazole, Diethylcarbamazine, Mebendazole, Niclosamide (for tapeworms), Suramin, and Thiabendazole.The Piperazine family includes many effective Antihelmintic. Black walnut, clove (*Syzygiumaromaticum*), wormwood (*Artemisia absynthium*), tansy tea (*Tanacetumvulgare*) and male fern (Dryopterisfilix –mas) are examples of plants that naturally contain helminthes inhibitors as shown in **Figure.1**

Figure:1 Antihelmintic Forms

Synthesis official drugs

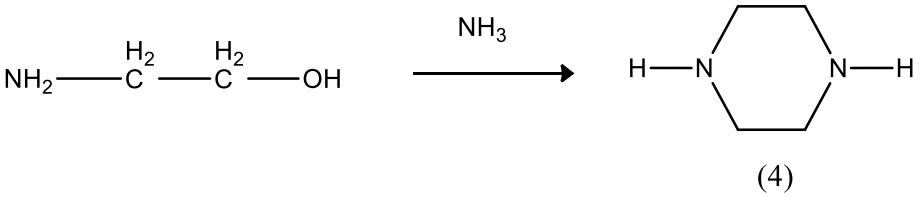
1. Albendazole: Albendazole is synthesized by heterocyclizing a phenylendiamine derivative into a benzimidazole derivative, methyl-[5-(propylthio)-1H-benzoimidazol-2-yl] carbamate (2). This process begins with 3-chloro-6-nitroacetanylide (1), whose nitro group is reduced with hydrogen using a palladium on carbon catalyst, producing 4-(propylthio)-o-phenylenediamine (2). The resulting o-phenylenediamine derivative is then treated with cyanamide followed by methyl chloroformate to yield albendazoleis produced [4]. As seen in Scheme 1



Scheme: 1 Synthesis of Albendazole

Albendazole is a wide-spectrum antihelmintic drug that belongs to the benzimidazole class of compounds. By inhibiting the parasites' ability to absorb glucose, it has an antihelmintic impact on sensitive cestodes and nematodes.

2. Piperazine: In organic synthesis, piperazine (4) is a bulk product. It is created by heating ethanolamine in ammonia between 150 and 200 degrees Celsius and between 100 and 250 atmospheres of pressure. Usually in the form of adipinite, it is utilized as a medication in the form of a salt [5,6] as shown in Scheme:2

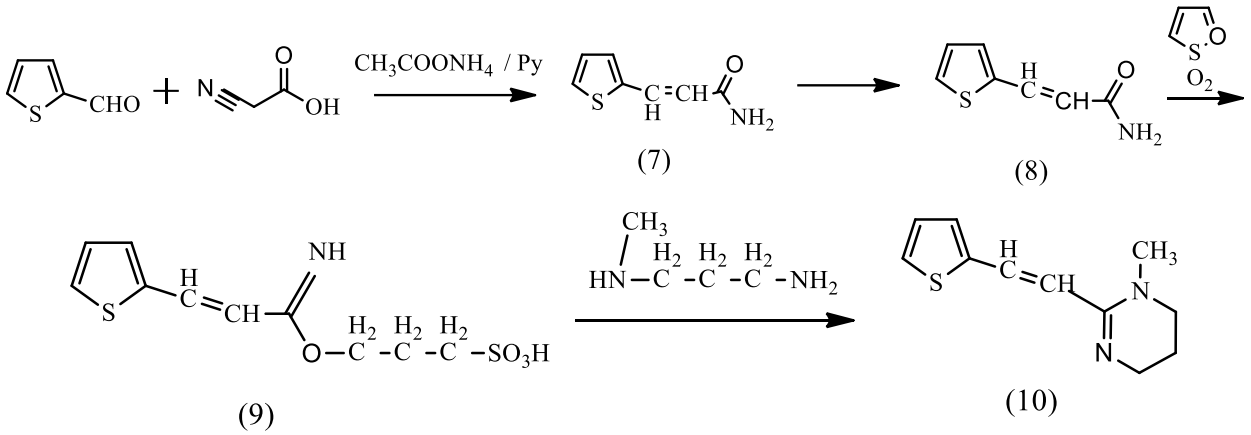


Scheme: 2 Synthesis of Piperazine

The alternative medication piperazine is used to treat a variety of worm diseases, especially ascariasis and enterobiasis. It stops cholinergic transmission, which paralyzes the worm. The parasite separates from the mucous membrane as a result, and the body eliminates it.

3.Pyrantel: The tetrahydropyrimidine derivative pyrantel (1,4,5,6-tetrahydro-1-methyl-2-[trans-2-(2-thienyl)vinyl] pyrantel) is synthesized from 3-(2-thienyl)-acrylonitrile (10), which is formed through a Knoevenagel condensation between

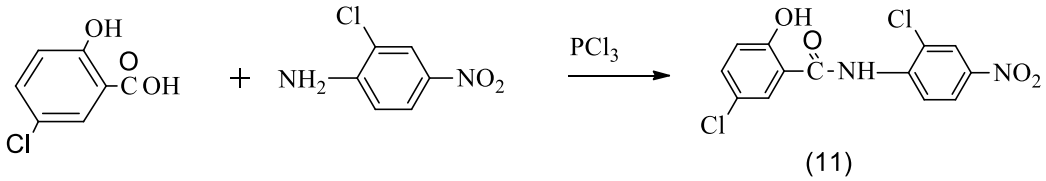
furfural and cyanoacetic acid. The acidic hydrolysis of this compound yields 3-(2-thienyl) acrylamide (8). When propansulfone reacts with this, an iminoester (9) is produced, which then reacts with N-methyltrimethyl-enediamine to form the desired pyrantel.[7-10] as depicted in scheme 3.



Scheme: 3 Synthesis of pyrantel

Pyrantel is a very good antihelmintic medication for nectoriasis, ankylostomiasis, ascariasis, and enterobiasis. By binding to their cholinergic receptors, the anthelmintic effect appears as a strong cholinomimetic effect on nematode muscle cells.

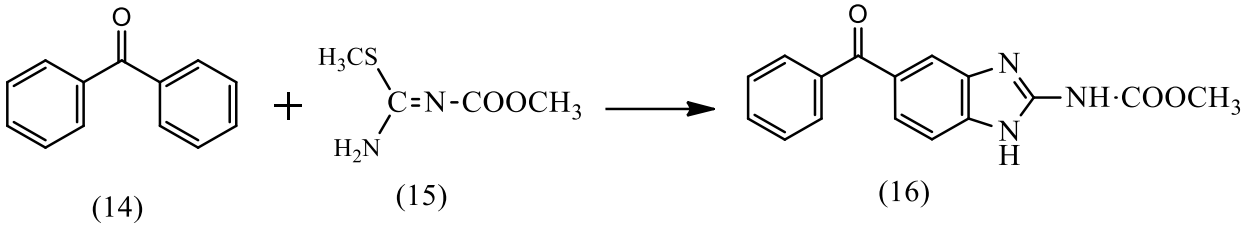
4. Niclosamide: When 5-chlorosalicylic acid and 2-chloro-4-nitroaniline react with phosphorus trichloride present, niclosamide, 2', 5-dichloro-4'nitroaniline (11), is produced. As shown in the scheme: 5, [11-13]



Scheme: 4 Synthesis of Niclosamide

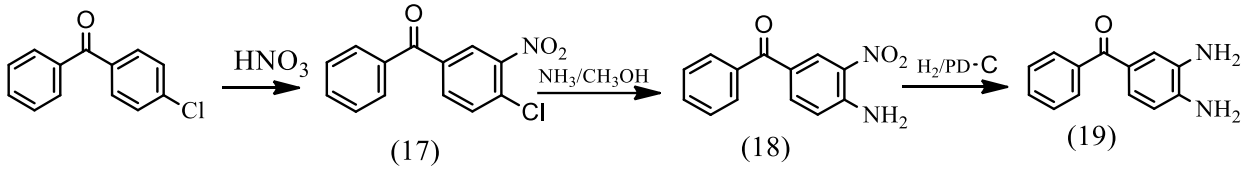
A powerful antihelmintic medication, niclosamide is a derivative of salicylamide. In both parasites and mammals, it works by inhibiting mitochondrial oxidative phosphorylation. It simultaneously prevents the parasite from absorbing glucose and oxygen. It essentially has no pharmacological impact on the host organisms at therapeutic levels. Niclosamide works well against intestinal cestodes such *Dipilidium caninum*,*Taenia solium*, *Diphyllobothium la-tum*, and *Hymenolepisdiminuta*, but it doesn't work well against nematodes.

5.Mebendazole: Methyl-[5-(benzoyl)-1-H-benzimidazol-2-yl] mebendazole, when 3,4-diaminobenzophenone (14) and N-methoxycabonyl-S-methylthiourea (15) combine, carbamate (16), a derivative of benzoimidazole, is produced. [14-15] as the scheme illustrates: 5 (a)



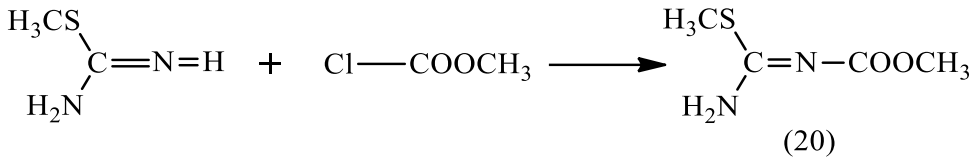
Scheme: 5 (a) Synthesis of Mebendazole

The following process is used to create the required reagents. 4-chlorobenzophenone is nitrated with nitric acid at a temperature below 5°C to get 4-chloro-3-nitrobenzophenone (17). 4-amino-3-nitrobenzophenone (18) is produced by heating 4-chlorobenzophenone to 125°C in a solution of ammonia in methanol, which substitutes an amino group for the chlorine atom by employing a palladium-on-carbon catalyst to reduce the nitro group in this molecule with hydrogen, 3,4-diamino benzophenone is produced (19), as seen in the scheme:5,(b)



Scheme: 5(b) Synthesis of Mebendazole

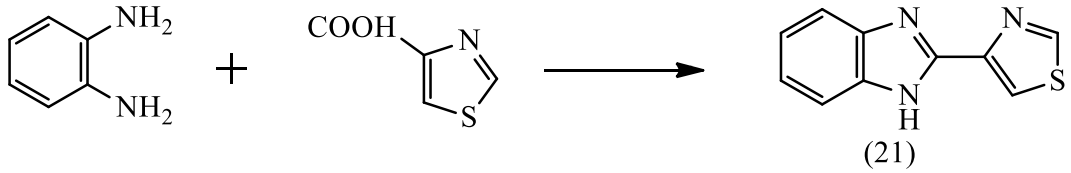
The reaction of methyl chloroformate with S-methylthiourea (20) yields the second reagent, N-methoxycarbonyl-S-methylthiourea, as illustrated in the following scheme: 5 (c)



Scheme: 5(c) Synthesis of Mebendazole

Although precise mode of action of Mebendazole is unknown, it is thought to be an irreversible suppression of the parasite's uptake and consumption of glucose, which also prevents the production of ATP, leading to the depletion of glycogen and eventual parasite death. Mebendazole is used to treat *trichocephaliasis, trichuriasis, ankylostomiasis, enterobiasis, ascariasis*, and mixed helminth infections.

6. Thiabendazole: As seen in scheme 6,Thiabendazole, 2-(4'-thiazolyl) benzimidazoles (21), is also produced by the same process of hetero-cyclization that takes place when o-phenylenediamine reacts with 1,3-thiazol-4-carboxylic acid [16-18].



Scheme: 6 Synthesis of Thiabendazole

Thiabendazole is a broad spectrum Antihelmintic medication. Its precise mode of action is unknown, however it appears to be mediated by the suppression of *fumarate reductase*, a particular helminth enzyme. Most nematode infections, such as those caused by *Angyostrongluscantonesis, Stronguloidesstercoralis, Trichinellaspiralis, Toxocaracanis, Toxocaracati, Ancylostoma caninum*, can be treated with thiabendazole.

Mechanism of action [19]

Benzimidazole

The first member of this class, Thiabendazole, was identified in 1961. As broad spectrum Anthelmintics, several other benzimidazoles were also introduced. Many diverse biochemical effects of these substances have been reported in a large body of literature. However, it is evident that their helmintic potency stems from their capacity to undermine the cytoskeleton via a deliberate engagement with β-tubulin [19, 20]. In all examined mammalian species, Benzimidazole anthelmintics undergo significant metabolism. Drug in this class include albendazole, mebendazole, and thiabendazole [21].It inhibits the growth of microtubules.Since many helminth species have shown that benzimidazole reduces glucose uptake both in vitro and in vivo, early studies on the mechanism of action of these chemicals focused on their role in carbohydrate metabolism. It has been demonstrated that Albendazole inhibits the intake of glucose by sensitive parasites in both larval and adult stages, reducing their glycogen stores and ATP synthesis, ultimately resulting in the parasite's death [24]. The cytoplasmic microtubules of the intestinal and tegument cells of cestodes and nematodes are removed by Mebendazole [21–25] and flubendazole [25]. This is followed by a decrease in the intake of glucose and an increase in the use of stored glycogen, as well as a loss of secretory vesicle transport.

Albendazole, which has a chemical structure similar to that of Mebendazole (MBZ), is distinguished by its ability to penetrate the blood-brain barrier. This property enables it to effectively combat parasitic infections affecting the central nervous system and may offer potential in treating brain metastases. It is a widely used broad-spectrum antiparasitic agent, effective against various parasitic infections across the globe [22–24]. Studies on the action mechanism of benzimidazoles (BZs) indicate that these drugs work by inhibiting microtubule formation through binding to tubulin [19-25]. It has been demonstrated in

experiments and clinically settings that inhibitors of microtubule polymerization have beneficial anticancer action.[26]. Benzimidazole (BZD) methylcarbamate molecule, Albendazole (ABZ) demonstrates strong activity against a wide range of helminth parasites, such as lung worms and the adult and larval stages of the majority of gastrointestinal (GI) nematodes, cestodes, and trematodes. [27] Human Antithetic activity several clinical experiments have been carried out to determine the effectiveness of Albendazole in treating human nematodes and cestode infections. [28-31].These trails findings suggest that Albendazole is a potentially useful single dose medication for treating *Ascaris lumbricoides, Necator americanus, Ancylostoma duodenale*, *Trichuris, and Enterobius vermicularis*.

Macrocyclic Lactones and Milbemycins

Avermectin

The identification of the avermectins, a chemically unique class of anthelmintics [32] presented a pleasant substitute. But since its debut in the early 1980s, it has been determined that sheep nematodes are resistant to Ivermectin, one of these chemicals. Avermectins are a class of macrocyclic, broad – spectrum lactone antibiotic antagonists that are used to treat nematodes parasites in both humans and animals, [33] and considered to operate in both cases using the same mechanism. [34] They are used to treat respiratory,cardiac, and gastrointestinal nematodes parasites in domestic animals as well as onchocerciasis, or river blindness, in people. Avermectins selectively paralyze parasites by increasing muscle Cl permeability,nevertheless, there has been debate on which channel the avermectins target. [35] The avermectins cause pharyngeal pumping to become paralyzed by increasing the opening of glutamate–gated chloride (glucose) channels.

Structure Activity Relationship (SAR) of Benzimidazole

The biological assessment and synthesis of some 2-phenyl benzimidazole-1-acetamides for their anthelmintic properties. In comparison to the common Albendazole, some of the series' compounds were found to be more effective at paralyzing worms, while others were more effective at causing worm death. Compound 29 proved to be the most effective among the series in both paralyzing and killing worms [36], as illustrated in Figure 2(a) during the SAR research.

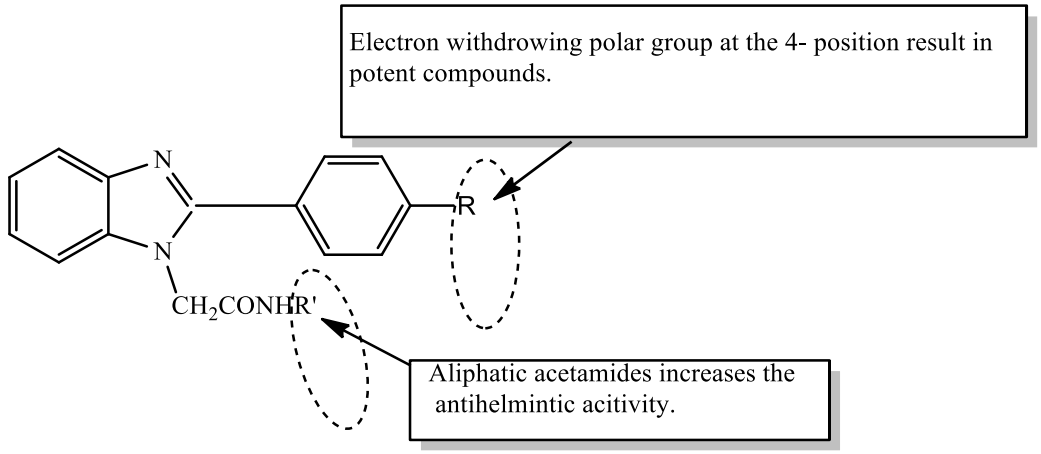


Figure: 2(a) SAR of Benzimidazole

Cd	R	R'	Paralysis time (min)	Death Time(min)
29 Albendazole	NO_2	Et	14.60(+)(-)5.53 21.43(+)(-)1.16	47.22(+)(-) 1.03 55.44(+)(-)1.65

According to Palomares-Alanso et al., novel benzimidazole derivatives were synthesized and showed in vitro cytocidal efficacy against Taenia crassiceps cysts. Compounds 31 and 30 showed satisfactory action. Molecular modeling studies suggest that for cysticidal activity, the molecule should feature an orthogonal substituent at position 5, a methyl carbamate group at position 2, and a hydrogen atom at position 1, as shown in Figure 2. (b) [37].

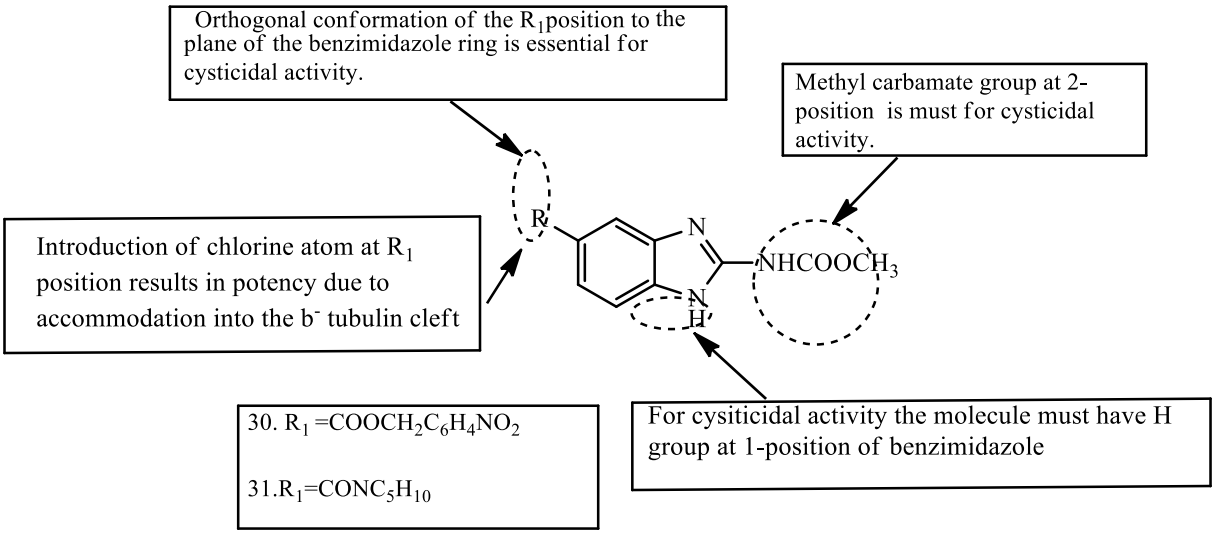


Figure: 2(b) SAR of benzimidazole

Praziquantel

Praziquantel has been used as a treatment since the 1980s, but it still has several drawbacks, including resistance, low solubilityand several side effects [38-41]. For this reason, additional research is required to produce a second generation of antischistosomal agents or novel antischistosomal agents that can be used in place of praziquantel in cases of resistance. Many primary methods can be used to generate such medications: (a) the production of PZQ analogs, (b) the logical development of novel Pharmacophores, and (b) the large-scale discovery of novel compounds through screening programs. [42-44]. Praziquantel molecule contains five locations that are prone to chemical transformations. As seen in figure 4 [45],

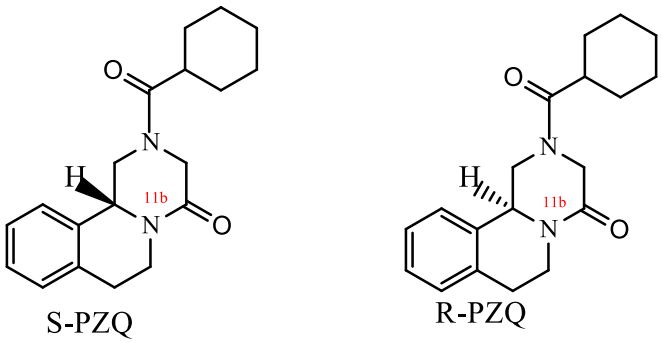
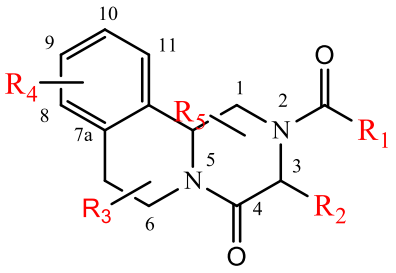


Figure: 3 Analogues of praziquantel



Possible variations in the structure of praziquantel

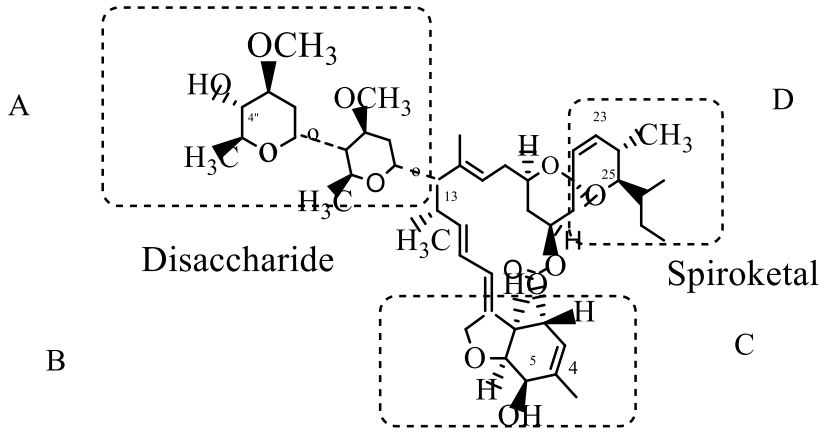
Figure: 2 SAR of Praziquantel

Although it is unclear how these adjustments were held, only the R1 position made significant investments in the original report and patent, as well as the activity displayed by its derivatives.[46]as shown in Figure :3.

Natural Product (Avermectin)

It may be seen from the analysis of avermectin's physiochemical characteristics and structure-activity relationship that the compound's sixteen-membered ring serves as the site of its insecticidal activity. It has been demonstrated that the activity of 16-ring to 18-ring macrolide compounds decreases with enlargement[47]. The structural characteristics of the macrocyclic core are mainly preserved in the modified avermectin (Figure 5). Modifications include:

- Functionalization of hydroxyl groups at C5, C4", and C23.
- Side chains at C4 and C25 on the large spiroketal moiety.
- A disaccharide group attached to C13.



The 16-ring macrolide contributes greatly to the activity

Figure: 3 SAR of Avermectin

"A" represents–Alkylamino, Hydroxyimino, Oxime Substituted C4" with different activates.

"B"Repesents -Disaccharide <monosaccharide>aglyconeF, Cl or MeO substituted disaccharide >OH, NH2substituted disaccharide

"C" Represents – Removing C5-OH reduce the activity; C5=NOR substituted C5-OH main the activity; C3, C4expoxides increases photo stability; Change C3=C4 to the C4=C4a reduce toxicity.

"D" Represents- Change C22=C23 to the C23=C24 increase Nematicidal activity, cyclic groups replace C25 increases the activity against certain pests.

The essential component for avermectins' insecticidal action is the hydroxyl group on C5 of the hexahydrobenzofuran ring. The hydroxyl group in this location has the potential to establish a hydrogen bond with GluCl, according to reports [48].

Macrocyclic Lactone Resistance

The term "avermectin and milbemycin resistance" is commonly used to describe ML-resistant worm populations. Ligand-gated chloride channels are considered the primary targets of ML therapy, and mutations in the genes encoding these channels may lead to resistance (AR). Initial reports of mutations in the GluCIR gene came from studies investigating the resistance of parasitic worms to Ivermectin. It was found that an allele of the GluCla-subunit gene was more commonly present in Ivermectin and Moxidectin-resistant isolates of *Haemonchus contortus*, suggesting a link between mutations in this gene and ML resistance. [49-50]. P-glycoproteins (Pgps) are transport proteins that function as an efflux mechanism, pumping molecules out of the cell and lowering their concentration inside. This prevents the medication from reaching its intended target.Macrocytic lactone resistance is most likely caused by enzymes involved in drug metabolism. In contrast to a susceptible isolate, Yilmaz*et* al.[51]

Resistance to Benzimidazoles

The way that benzimidazole works a definite link has been shown between changes in β-tubulin and antihelmintic resistance. Benzimidazole resistance may result from the isotype l β-tubulin's phenylalanine 200-tyrosine alteration. [51].The tubulin protein can be mutated by just one amino acid, which prevents resistant nematodes from binding to benzimidazole.These three nonsynonymous single nucleotide polymorphisms (SNPs) in the isotype 1-tubulin gene have been linked to benzimidazole resistance in gastrointestinal nematode (GIN) species.

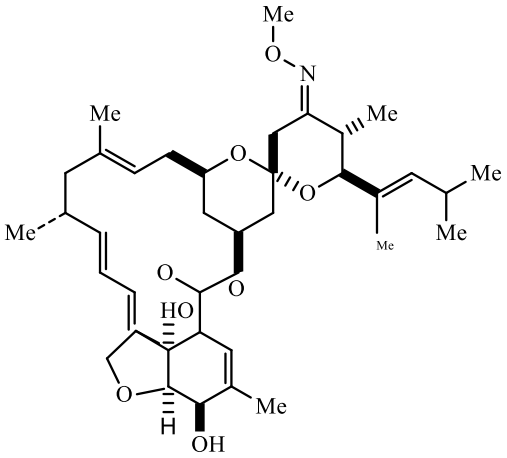
Resistance to imidothiazoles and tetrahydropyrimidines

Nicotinic acetylcholine receptors (nAChRs), especially the L-type subgroup, which are activated by pyrantel and levamisole, have been investigated to understand how resistance to nicotinic agonists develops. Activation of these L-nAChRs leads to neuromuscular depolarization and spastic paralysis. Resistance to levamisole and pyrantel in different Trichostrongylid nematodes appears to be mainly linked to changes at the drug target site. In *Haemonchus contortus*, *Teladorsagia colubriformis*, and *Trichostrongylus circumcincta*, resistance to these drugs has been associated with decreased expression of genes encoding nACh receptor subunits. Additionally, the presence of shortened forms of two receptor subunits—unc-63b (a truncated version of unc-63a) and acr-8b (a truncated version of acr-8a)—has been linked to resistance. [53-54]

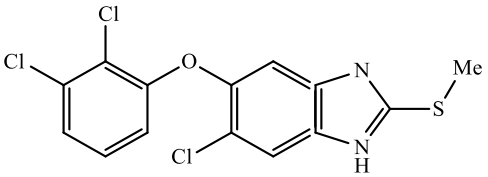
Commercial Incentives for Antihelmintic Development

The Pharmaceutical industry, probably for financial gain, has mostly disregarded these indications despite the critical need for novel medications and other control measures for human helminth infection. In fact, between 2000 and 2011, no new chemical entities were approved. [50-51] Since then, the only medications that have been approved are Triclabendazole andMoxidectin. Diethylcarbamazine, praziquantel, mebendazole, albendazole, and avermectin are the primary drugs used to treat human helminth infections, and they have been used in clinical settings for a long time.The lack of innovative medications is a reflection of the low financial return on investment for neglected tropical Illnesses like human helminth infection.Proposals to encourage these kinds of investments have been made. Developing innovative medications for disease that would otherwise go untreated is intended to be financially motivated by the FDA Tropical Disease Priority Review Voucher Program.[55,56]. Organizations that successfully obtain approval for an eligible medicine are granted a transferrable voucher good for a significant additional priorityreview. Two anthelmintic medications have recently benefited from this program: Triclabendazole approved for fascioliasis (infection with the liver fluke *Fasciola hepatica*) and Moxidectin which demonstrated superiority to avermectin for onchocerciasis.

New anthelmintic Drugs developed via FDA Tropical Disease Priority Review Voucher Program

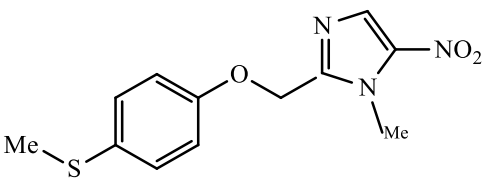


Moxidectin

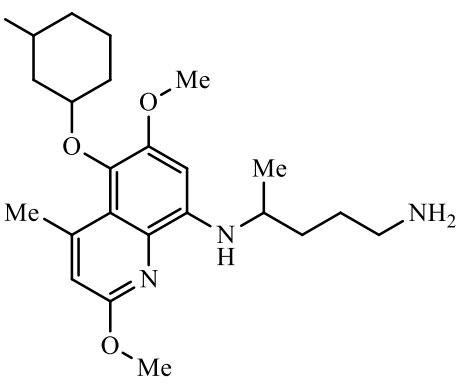


Triclabendazole

New drugs and drug candidates for other neglected diseases have been developed through public-private partnership (PPP) initiatives.



Fexinidazole



Tafenoquine

Figure: 4 Structures of new anthelminthic drugs developed through repurposing and new drug or drug candidates for other neglected disease developed through public-private-partnership (PPP) initiatives.

Future Scope of Antihelmintic Drugs

Due to the cost-effectiveness and important of the anthelmintic medication market, the rich segment of the pharmaceutical industry does not share the difficulties faced by enterprises involved in Antihelmintic drug conduct. For the most part, tropical medicine requires that Anthelmintics be utilized in chemotherapy programs in areas with limited clinical care and that medications be extremely well–tolerated by people. Over the past two decades, a limited number of medications, particularly Ivermectin, have met the demand, and it has been extremely effective in both tropical and veterinary medicine. The most significant worry for the future is the rise in resistance to all currently used Anthelmintics, including Ivermectin, which is essential in determining the mode of action for most of these medications and can also help determine the mechanisms of resistance, particularly when the "model-hopping" approach. The issue of anthelmintic resistance is anticipated to be resolved in the future by new Anthelmintics with unique mechanisms of action. The underlying information is being provided by more focused to techniques for Antihelmintic drug development, which are also underway and do not attempt to target the peptidergic signaling pathways that resulted in a commercially viable medication.

2. CONCLUSION

There are presently only a few anthelmintic medications on the market. Because of their restricted range of action, safely concerns, high cost or unfeasible delivery methods, many of them are not particularly helpful. Because of unforeseen issues like the emergence of medication resistance, which requires more attention than it currently receives, some of these will be terminated. Medicine development takes a lot of effort and before a medicine is ever used in clinical trials, it must pass rigorous interdisciplinary interactions amongst researchers utilizing the most exacting quantitative tests to establish toxicity, safety, mechanism of action, and pharmacokinetics. It is necessary to set up a set of universal testing guidelines that are approved by everyone working on medication development. In order to create novel chemicals, scientists are starting to use rational design, and this strategy should be used more often in the future. Clinically, things are beginning to improve for the millions of people who are afflicted with helminth infections because of the availability of broad range chemicals that may be used in clinics and mass treatment programs.

Abbreviations:

PPP- Public Private Partnership;**PZQ**- Praziquantel; **GI**- Gastrointestinal; **ABZ**- Albendazole ;**Pgps**- P- glycoproteins; **nAChRs**- Nicotinic acetylcholine receptors; **GIN**- Gastrointestinal nematode; **SNPs**- Single nucleotide polymorphisms; **NTDs**- Neglected Tropical Disease; **MBZ**- Mebendazole; **SAR**- Structure Activity Relationship; **SNPs**- Single Nucleotide Polymorphisms

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Conflict of interest

There are no conflicts to declare

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