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ADVANCED SYNTHETIC ENTITIES PENETRATING IN THE HELMINTHIASIS REMEDY: AN EXTENSIVE REVIEW

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ABSTRACT

Helminthiasis, a parasitic worm infection, is caused by Helminthic parasites like flatworms, pinworms, roundworms, hookworms, tapeworms, etc. There are many potential drugs available for the treatment of Helminthiasis. Albendazole and a few other benzimidazole derivatives are one of them. Albendazole has adverse effects like stomach pain, nausea, vomiting, headache, dizziness, and reversible hair loss. Further, consumption of such drugs in children may lead to severe adverse effects such as fever, chills, sore throat, mouth sores, light-headed feeling, seizure, ringing in the ears, vision problems, increased pressure inside the skull, and pain behind the eyes. This drug is contraindicated in pancytopenia, low blood count due to bone marrow failure, anemia, liver problems, low WBC count, and pregnancy. Therefore, a substantial unmet need is required to develop some advanced anthelmintic agents with minimal adverse effects.

Keywords: Fascioliasis, Trypanosomiasis, Onchocerciasis, Neurocysticercosis, Theileriosis, Endoectocide

INTRODUCTION

Helminthiasis, also termed worm infection, is a macro parasitic disease in which body part is affected by helminths or parasitic worms. Helminths are of different types like

flatworms that include tapeworms and flukes, pinworms, roundworms, and hookworms. This can reside in the digestive tract of a host. Helminths can either live in tissues or their larvae migrate into tissues. Helminths can harm the hosts by depriving food, loss of blood, injury to organs, obstruction in the lymphatic system or intestine, and secretion of toxins. Depending on the severity of the infection, Helminthiasis may be fatal or not, but this plays a broader role in the illness. This is often seen in developing countries having poor personal and environmental hygiene. Several like consuming contaminated water, contaminated soil, and contact with contaminated faeces, poor sanitation, or poor hygiene can cause Helminthiasis. **Figure 1** shows pinworms and tapeworms.

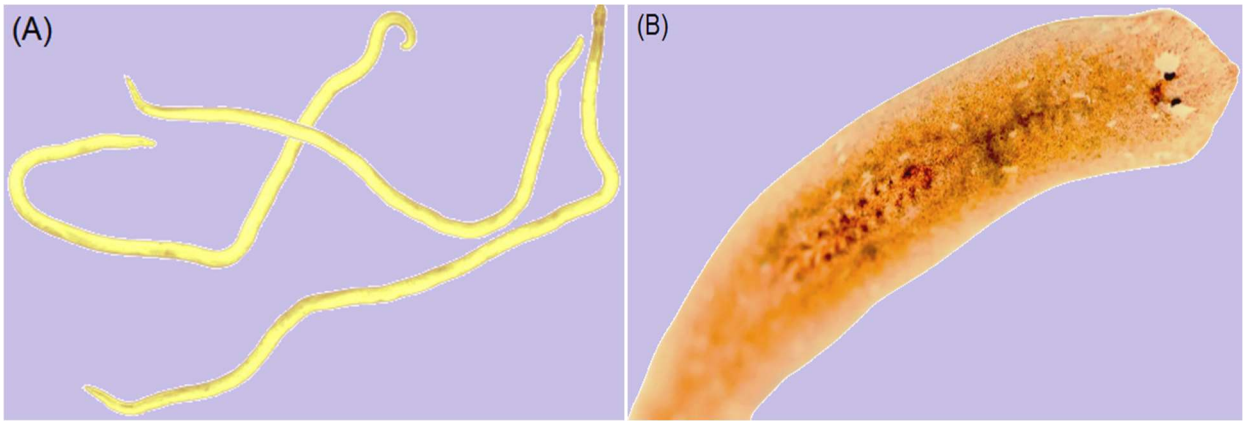


Figure 1: (A) Pinworms (B) Tapeworms

Signs and symptoms of Helminthiasis include nausea, vomiting, abdominal pain, diarrhoea, loss of appetite, visibility of worms in stools, weight loss, gas, bloating, tenderness, etc.

Helminthiasis can be well treated by several i) Benzimidazole derivatives like Albendazole, Mebendazole, Thiabendazole ii) Quinoline and Isoquinoline derivatives like Oxamniquine and Praziquantel iii) Piperazine derivatives like Piperazine citrate and Diethylcarbamazine citrate iv) Vinyl pyrimidines like Oxantel and Pyrantel pamoate v) Amides like Niclosamide vi) Natural products like Avermectins, Ivermectin, Doramectin, Selamectin, and Abamectin vii) Organophosphorous derivatives like Metrifonate viii) Imoidazothiazoles like Levamizole ix) Nitro derivatives like Niridazole. Benzimidazole derivatives like Albendazole, Mebendazole, and Thiabendazole bind to the colchicine-sensitive binding site of β-tubulin, inhibit polymerisation and inhibits the formation of microtubules. This will cause degenerative

changes in the intestinal cells of the worms. Benzimidazoles bind far better to β-tubulin of the parasites than mammals **[1-3]**. **Figure 2** shows the structures of some popular anthelmintic drugs currently available in the market.

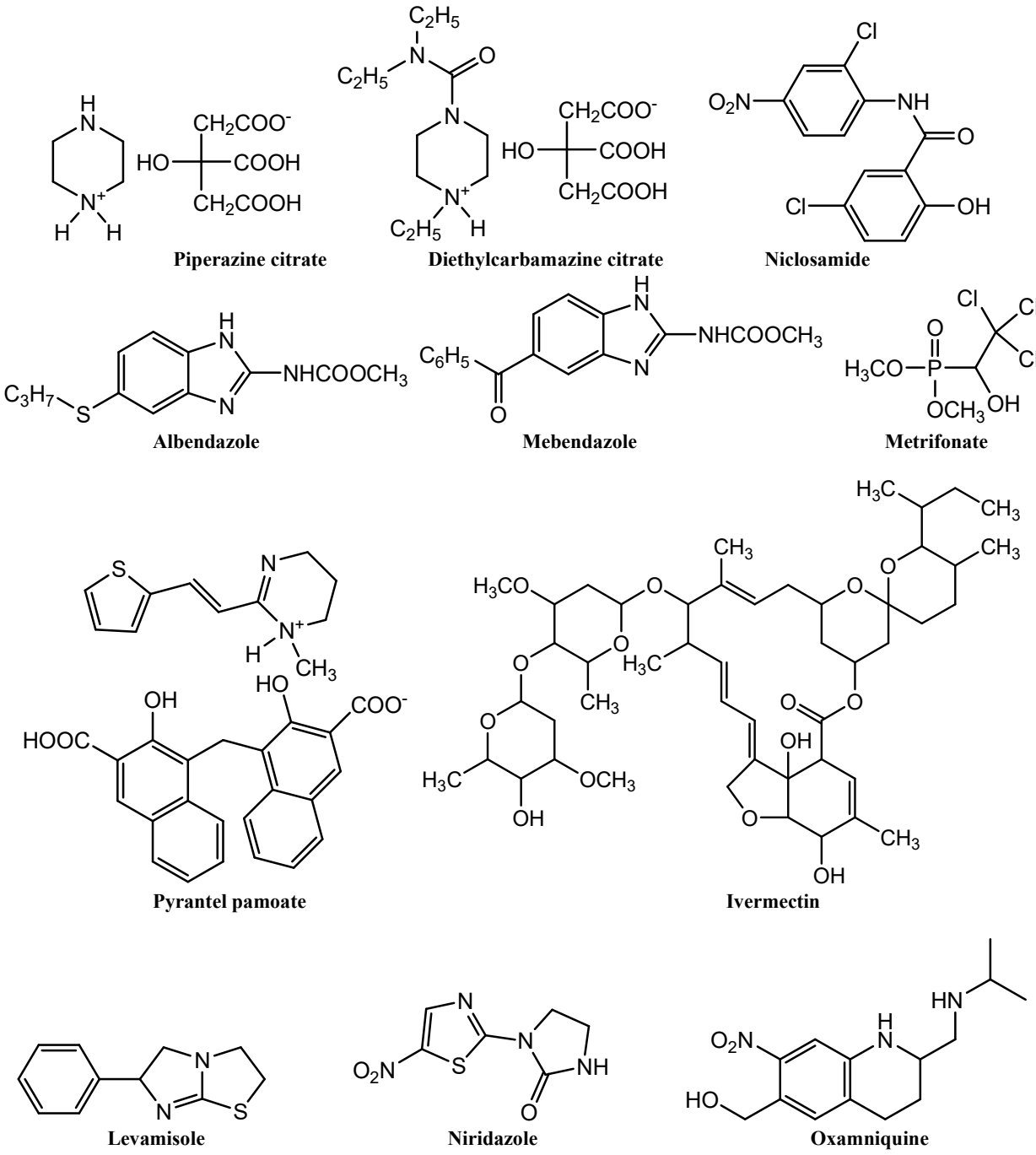


Figure 2: Structures of anthelmintic drugs currently available in the market

Adverse effects, contraindications, and resistance of Albendazole, other benzimidazole derivatives, as well as currently available anthelmintic agents

Albendazole cause much more side effects like stomach pain, nausea, vomiting, headache, dizziness, and reversible hair loss. Also, in the child, it can cause fever, chills, sore throat, mouth sores, light-headed feeling, seizure, increase in the pressure inside the skull, ringing in the ears, vision problems, and pain behind the eyes. Also, this drug cannot be given in case of pancytopenia, low blood count due to bone marrow failure, anemia, liver problems, low WBC count, and pregnancy. Further, resistance has been developed with currently available anthelmintic agents, creating an enormous urge to design and develop newer agents that can treat Helminthiasis well with lesser adverse effects **[4]**.

The purpose of the study

In the present review, we have incorporated some newly invented anthelmintic agents. The main aim of the current study is to give new directions for anthelmintic drug discovery and development. Researchers can able to take benefit from these newly invented medicaments. Researchers have discovered some novel scaffolds and heterocyclic rings to develop anthelmintic agents. Various heterocyclic rings like pyran, morpholine, benzimidazole, imidazole, quinoline, indole, dioxoepine, pyrazole, isoxazole, and benzothiazole have reflected they're much more critical in the anthelmintic research. Also, during the upcoming decades, researchers can take some benefits of these essential scaffolds for the anthelmintic drug investigation purpose.

Newly invented anthelmintic drug agents

Pyran derivatives

ABBV-4083 (TylAMac)

Chemically ABBV-4083 or TylAMac is a derivative of veterinary antibiotic tylosin **(Figure 3)**. This drug has completed a phase III clinical trial. von Geldern TW *et al*. have identified a newer macrofilaricidal agent, Tylosin A, that targets worm-symbiont *Wolbachia* bacterium. They Chemically modified Tylosin A and obtained a drug candidate, ABBV-4083, with higher anti-*Wolbachia* activity and anti-filarial activity with improved pharmacokinetic properties. It can kill adult worms selectively and is used to treat onchocerciasis **[5]**. Hubner MP *et al*. have determined *Wolbachia* depletion kinetics with different concentrations. They have observed *Wolbachia* reduction in mice three days after the initiation of ABBV-4083 **[6]**.

Moxidectin

It is chemically (1R,4S,4'E,5'S,6R,6'S,8R,10E,13R,14E,16E, 20R,21R,24S)-21,24-Dihydroxy-4'-methoxyimino-5',11,13,22-tetramethyl-6'-[(E)-4-methylpent-2-en-2-yl]spiro [3,7, 19-trioxatetra cyclo[15.6.1.14,8.020,24]pentacosa-10,14,16,22-tetraene-6,2'-oxane]-2-one **(Figure 4)**. This drug has currently approved by USFDA for the treatment of onchocerciasis **[7]**. Cobb R *et al*. have informed a second-generation macrocyclic lactone-containing drug Moxidectin with potent endectocide activity. This drug is present as an oral gel formulation, and it is used to kill parasites in horses. Cobb R *et al*. have reported that this drug gives its action by binding with gamma-aminobutyric acid and glutamate-gated chloride ion channels. It is highly effective against all nematodes. They have enlightened that antiparasitic activity is further increased against cestodes when this drug is prescribed along with Praziquantel **[8]**.

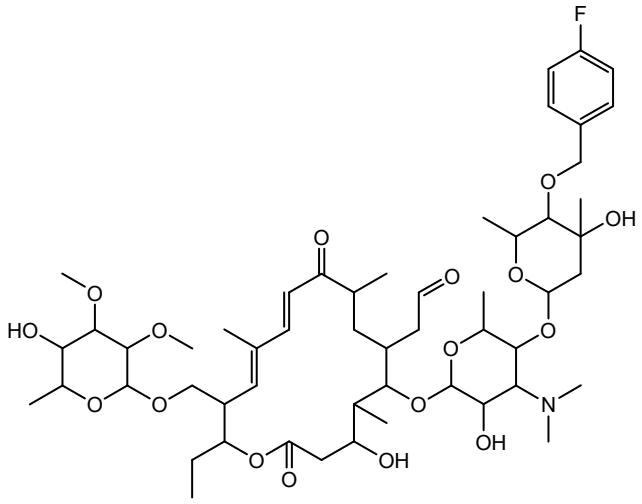


Figure 3: Structure of ABBV-4083 (TylAMac)

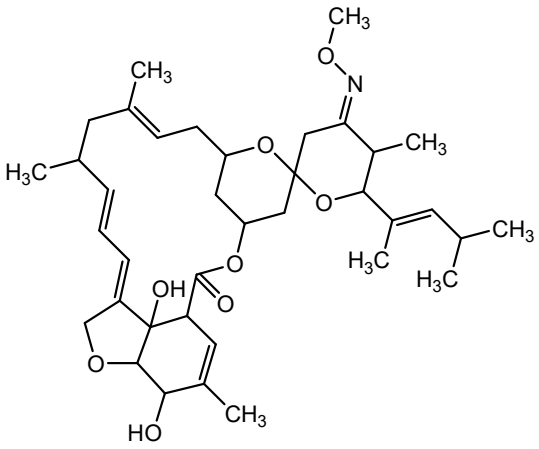


Figure 4: Structure of Moxidectin

Morpholine derivatives

Emodepside

Chemically it is a morpholine ring containing cyclo-octadepsipeptide analogue that shows parasitic and free-living nematodes paralysis **(Figure 5)**. Holden-Dye *et al*. have stated that emodepside creates extracellular calcium and efflux of potassium ions dependent hyperpolarisation of the body wall muscle. After broad studies on elegans and tissue-specific expression, they have addressed that Emodepside acts on SLO-1 in neurons regulating feeding and motility **[9]**. Krucken J *et al*. have addressed a novel mechanism with broad-spectrum activity against migrating larvae or microfilariae like extraintestinal nematode stages **[10]**.

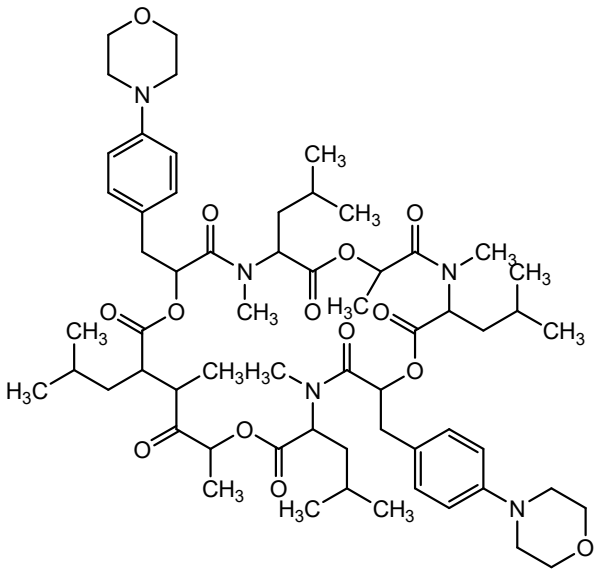


Figure 5: Structure of Emodepside

Benzimidazole derivatives

Triclabendazole

It is chemically 6-Chloro-5-(2,3-dichlorophenoxy)-2-methylsulfanyl-1-*H*-benzimidazole **(Figure 6)**. Gandhi P *et al*. have communicated a novel drug Triclabendazole approved in 2019 by USFDA to treat human fascioliasis in adults and children and all the stages and forms of infection **[11]**. Davis CN *et al*. have informed that fascioliasis, a neglected zoonotic disease, can be well treated by this halogenated benzimidazole derivative in the absence of a vaccine **[12]**.

Fenbendazole

It is chemically Methyl-*N*-(6-phenylsulfanyl-1-*H*-benzimidazol-2-yl)carbamate **(Figure 7)**. Yamaguchi T *et al*. have described that this drug has a broad spectrum of antiparasitic activity in dogs and pigs. The same agent also has antitumor effects as it inhibits microtubule-assisted tubulin polymerisation. Yamaguchi T *et al*. have made doubt about the safety and tolerability profile in humans that an 80 years old female with advanced nonsmall cell lung cancer has suffered liver injury after nine months by taking Fenbendazole drug for one month **[13]**. Ciuca L *et al*. have reported the effectiveness of Fenbendazole against *Giardia* infection in dogs and concluded that this drug is more effective with fewer adverse effects **[14]**.

Flubendazole

Chemically it is Methyl-*N*-[6-(4-fluorobenzoyl)-1-*H*-benzimidazol-2-yl]carbamate **(Figure 8)**. It is a 4-fluoro derivative of Mebendazole in which the 4-fluorobenzoyl group replaces the benzoyl group. Geary TG *et al*. have expressed that

this drug was approved in 1980 to treat gastrointestinal nematode infections in veterinary and human medicine. They have informed that efforts have been made to discover and develop newer microfilaricides, particularly for the treatment of onchocerciasis. They have elucidated that research has been recently done to create more unique formulations with high oral bioavailability **[15]**. Kubicek V *et al*. have declared that due to binding ability with tubulin and low toxicity, Flubendazole has been considered to give anticancer activity **[16]**.

Oxfendazole

It is chemically Methyl-6-(phenylsulfinyl)-1-*H*-benzo[d]imidazol-2-ylcarbamate **(Figure 9)**. Gonzalez AE *et al*. have disclosed that this drug is effective against gastrointestinal lungworms and roundworms of livestock, adults, as well as L4-larvae of the species like *Haemonchus*, *Bunostonum*, *Nematodirus*, *Teladosargia*, *Trichostrongylus*, *Oesophagostomum*, *Ostertagia*, *Dictyocaulus*, *Trichuris* etc. **[17]** An G *et al*. have informed the use of the veterinary drug, Oxfendazole, against *Taenia solium* and informed that this drug is potentially active in the treatment of neurocysticercosis **[18]**.

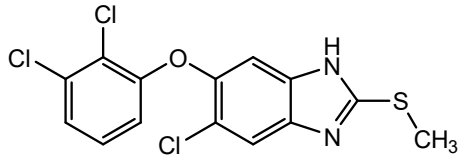


Figure 6: Structure of Triclabendazole

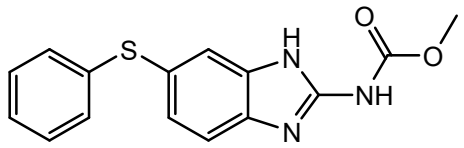


Figure 7: Structure of Fenbendazole

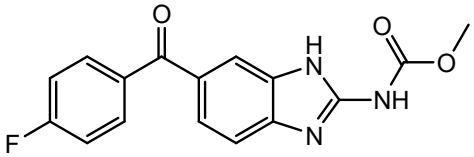


Figure 8: Structure of Flubendazole

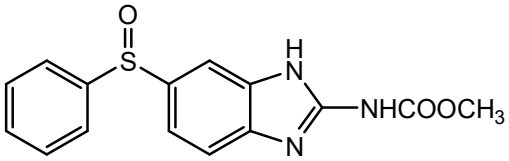


Figure 9: Structure of Oxfendazole

Imidazole derivatives

Fexinidazole

Chemically it is 1-Methyl-2-[(4-methylsulfanylphenoxy)methyl]-5-nitroimidazole **(Figure 10)**. Victor KB *et al*. have communicated that Fexinidazole, a 5-nitroimidazole derivative, is highly effective in treating the post-stage human African trypanosomiasis caused by trypanosomabruceigambiense (g-HAT) against a combination therapy of oral nifurtimox with intravenous eflornithine. The previous combination therapy that requires skilled personnel can be overcome by using Fexinidazole **[19]**. Deeks ED *et al*. have informed that Fexinidazole is the first global

approved DNA synthesis inhibitor drug. They have informed that this drug is developed in collaboration with Sanofi to treat sleeping sickness and Chaga's disease **[20]**.

Quinoline derivatives

Tafenoquine (SB-252263, WR238605)

Chemically, Tafenoquine is (4R)-4-*N*-[2,6-Dimethoxy-4-methyl-5-[3 (trifluoromethyl)phenoxy]quinolin-8-yl]pentane-1,4-diamine **(Figure 11)**. Badeliya SN *et al*. have published an 8-Aminoquinoline derivative, Tafenoquine, which can be used to prevent malaria and radical cure of *P. vivax* malaria **[21]**. In 2018, Jullian MD *et al*. evaluated all the available data on safety and efficacy and reported that this drug had been approved for malaria chemoprophylaxis **[22]**. Haston JC *et al*. have done the research and informed that in 2017, approximately 219 million malaria cases were reported, and among them, 4,35,000 deaths occurred **[23]**.

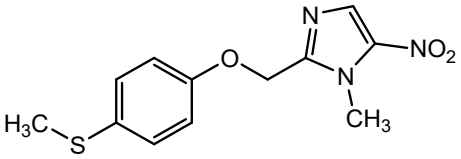


Figure 10: Structure of Fexinidazole

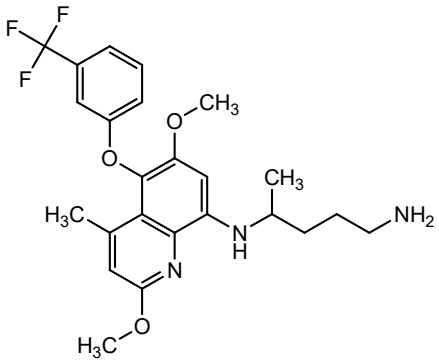


Figure 11: Structure of Tafenoquine

Indole derivatives

Derquantel

It is chemically (1S,6R,7R,9S,11R)-6-Hydroxy-4',4',6,10,10,13-hexamethylspiro[3,13-diazatetra cyclo[5.5.2.01,9.03,7]tetradecane-11,8'-9,10-dihydro-[1,4]dioxepino[2,3-g]indole]-14-one **(Figure 12)**. Puttachary S *et al*. have reported the effect of the combination of Derquantel with Abamectin on isolated tissues of *Ascaris Suum*. They have worked on a novel anthelmintic combination of Derquantel and Abamectin drugs and informed that these drugs interact pharmacologically. They have done the research and concluded that this combination affects somatic muscle nicotinic acetylcholine receptors and pharyngeal muscle glutamate-gated chloride receptor channels of *Ascaris suum* **[24]**. Little PR *et al*. have intimated the efficacy of derquantel in combination with abamectin against larval and adult stages of nematodes in sheep. They

have informed that this drug is active against anthelmintic-resistant strains **[25]**.

Pyrazole derivatives

Tolfenpyrad (MMV688934)

It is chemically 4-Chloro-3-ethyl-1-methyl-*N*-[4-(p-tolyloxy)benzyl]pyrazole-5-carboxamide **(Figure 13)**. Preston S *et al*. have performed *in vitro* anthelmintic activity against parasitic xL3 and L4 larval stages of *H. contortus*. They have calculated IC_{50} values of Tolfenpyrad and compared it with two standard anthelmintics, Monepantel and Moxidectin. Preston S *et al*. have reported that this pyrazole-5-carboxamide derivative has broad-spectrum activity against the egg, larval, nymphal, and adult stages of various arthropods like *Hemiptera*, *Acarina*, *Thysanoptera*, *Lepidoptera*, *Diptera*, *Coleoptera* **[26]**. Zhang CX *et al*. have studied the activity of Tolfenpyrad on *Chrysoperla Sinica* and described that this drug has minimum acute toxicity and sublethal effects on the development, reproduction, and predatory ability of *Chrysoperla Sinica* **[27]**.

Isoxazole and benzthiazole derivatives

Partridge FA *et al*. have intimated about CellProfiler, a major open-source tool for quantitative identification of active molecules from high-throughput screening **(Figure 14)**. Two molecules have been identified with *S. mansooni* thioredoxin glutathione reductase inhibitory activity by virtual screening. Partridge FA *et al*. have reported two small and safer molecules with identical activity against schistosomula and adult worms even at low micromolar concentrations **[28]**.

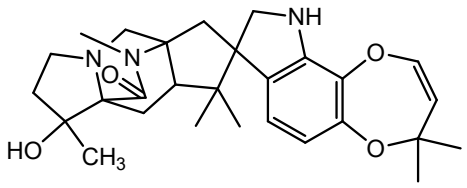


Figure 12: Structure of Derquantel

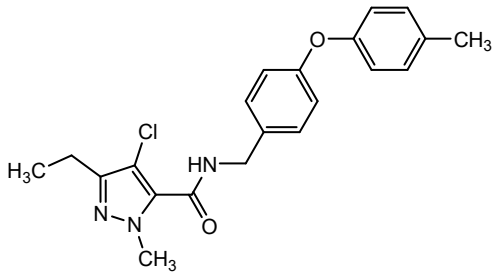
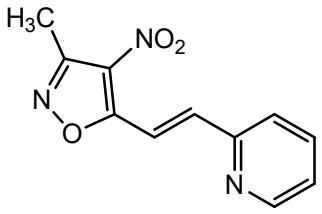
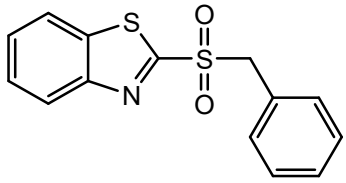


Figure 13: Structure of Tolfenpyrad



A) Isoxazole derivative



B) Benzthiazole derivative

Figure 14: Structures of A) Isoxazole and B) benzthiazole derivatives as anthelmintic agent

Others

PF1022A

Chemically it is an *N*-Methylated cyclooctadepsipeptide derivative and parent compound of Emodepside **(Figure 15)**. Sasaki T *et al*. have stated that the newly developed parent compound of emodepside is active against *Ascaridia galli* in chickens. It is a fermented product of the fungus *Rosellinia* species found on the leaves of *Camellia japonica*. It gives its activity against various intestinal stages of nematodes but is limited to parenteral stages that are not affected by this drug **[29, 30]**.

Buparvaquone

Chemically it is 3-[(4-*tert*-Butylcyclohexyl)methyl]-4-hydroxynaphthalene-1,2-dione **(Figure 16)**. Muragari GR *et al*. have disclosed that Buparvaquone is a hydroxynaphthoquinone derivative, and it is highly curative. They have studied the effect of this drug on 16 calves and reported that all the calves were cured by one injection of Buparvaquone in a dose of 2.5 mg/kg body weight **[31]**. Ibrahim E *et al*. have reported that Buparvaquone is the effective agent for the treatment of pregnant cows infected with bovine Theileriosis **[32]**.

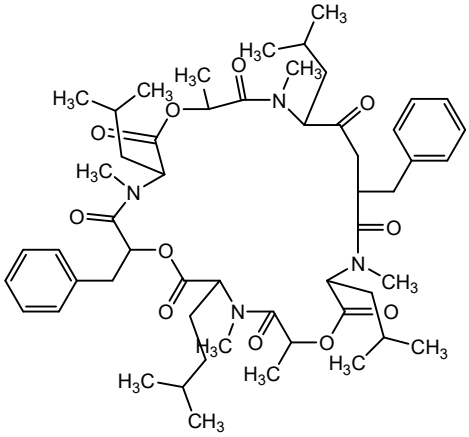


Figure 15: Structure of PF1022A

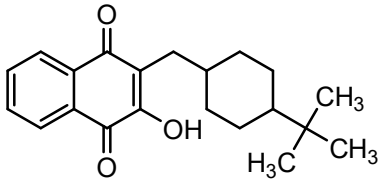


Figure 16: Structure of Buparvaquone

Monepantel (AAD 1566)

It is chemically *N*-[(2S)-2-Cyano-1-[5-cyano-2-(trifluoromethyl)phenoxy]propan-2-yl]-4-(trifluoromethylsulfanyl)benzamide **(Figure 17)**. The hookworm species *Ancylostomaduodenale* and *Necatoramericans*, the whipworm *Trichuristrichiura*, the threadworm *Strongyloidesstercoralis*, and roundworm *Ascarislumbricoides* are some of the examples of soil-transmitted helminths (STH) of great public health. Tritten L *et al*.

have informed that more than one billion people globally can be affected by these parasites, particularly in developing regions of Latin America, Asia, and Africa. This drug is highly effective in animals for the treatment of soil-transmitted helminthiasis. In humans, Monepantel has no *in vivo* activity against *N. americanus*, *T. muris*, *S. ratti*, and *A. suum*. Hence, this drug cannot be useful for treating soil-transmitted helminthiasis in humans **[33]**.

Pararosaniline hydrochloride

It is chemically [4-[Bis(4-aminophenyl)methylidene]-1-cyclohexa-2,5-dienylidene]dianiline **(Figure 18)**. Elfawal MA *et al*. have reported the activity of two pairs of Sulconazole/Econazole and Pararosaniline/Cetylpyridinium on *A. ceylanicum* infections in hamsters. They have concluded that Pararosaniline showed a marked effect on soil-transmitted nematodes like hookworms, whipworms, and *Ascaris in vivo* **[34]**.

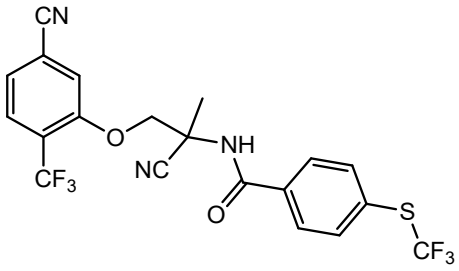


Figure 17: Structure of Monepantel

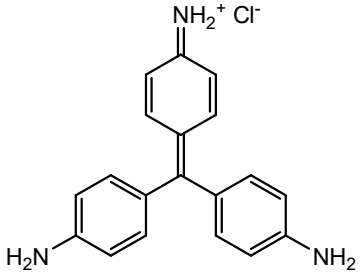


Figure 18: Structure of Pararosaniline HCl

CONCLUSIONS AND FUTURE PROSPECTIVES

The developed adverse effects, contraindications of Albendazole, other benzimidazole derivatives, and resistance against currently available anthelmintic agents have created a demand to design and develop some potential anthelmintic agents so that the adverse effects and contraindications can be overcome. Here we have performed a stipulated review of advanced potential anthelmintic agents. This review affirmed the effective drug candidates against various Helminthic forms with lesser side effects.

Abbreviations

WBC	: White blood cells
USFDA	: United States Food and Drug Administration
S. mansooni	: *Schistosoma mansooni*
g-HAT	: High annealing temperature
P. vivax	: *Plasmodium vivax*
H. contortus	: *Haemonchus contortus*
N. americanus	: *Necator americanus*
T. muris	: *Trichuris muris*
S. ratti	: *Strongyloides ratti*

A. suum : *Ascaris suum*

A. ceylanicum : *Ancylostoma ceylanicum*

Human and animal rights

No animals/humans were employed in the studies interpreted in this review.

Conflict of Interest

The authors asserted no conflict of interest, financial or otherwise.

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