



5-ETHOXY IVERMECTIN: A DOMINANT ANTI-HELMINTHIC

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Abstract

The review is based on the 5-ethoxy ivermectin is a dominant anti-helminthics. The helminthics are the worm like parasites which produces many of cause of our body as well as the animals. The number of drugs is available on market to cure disease but the ivermectin shows is dominant anti-parasitic activity. The main disadvantage of ivermectin shows some kind of slow killing the parasite. So I was made the derivative of ivermectin called as 5-ethoxy ivermectin. The 5-ethoxy ivermectin is made of some type of chemical reactions below in the review. The derivative was made base on the structural activity relationship.

Keywords- Ivermectin, 5-ethoxy ivermectin, Anti-parasite, Ascaris, Derivative.

I. INTRODUCTION

The helminthes are worm-like parasites. The clinically similar groups are separated according to their general external shape and the host organ they inhabit. [1] There are both hermaphroditic and bisexual species. The complete classification is based on the inner and outer morphology of egg, larval, and mature stages. Helminthes is commonly known as worm. The helminthes are abortive indicated through elongated, flat or spherical bodies. In medically the flatworms or Platy helminthes (platy from the Greek root meaning "flat") include flukes and tapeworms. [1] These category are subdivided for convenience on the report of the host organ in which they reside, e.g., lung flukes, extra intestinal tapeworms, and intestinal roundworms.

Flukes-Adult flukes are leaf-shaped flatworms. Prominent oral and ventral suckers help maintain position in situ. Flukes are double gated except for blood flukes, which are bisexual. [2]

Tapeworms- Mature tapeworms are lengths, segmented, double gated flatworms that inhabit the intestinal lumen. Larval shapes, which are cystic or solid, inhabit extra intestinal tissues. Helminthes birth through egg, larval, and adult stages gives the names appeal to different larval helminthes. Understanding of the dissimilar stages in connection to their development is the basis for understanding the epidemiology and pathogenesis of helminthes infection, as well as for the diagnosis and treatment of patients protect these parasites. The contributions of various stages to disease are listed in Table 1 stages of helminthes. [1]

table 1: stages of helminthes

SR NO	HELMINTHES	EGGS	LARVA	ADULT
1.	Flukes	-ve	+ve	-ve
2.	Tapeworm	-ve	-ve	+ve
3.	Nematode	-ve	+ve	+ve

Different types of diseases are caused due to the worms

1. Ascaris
2. Ancylostoma
3. Guinea worm
4. Dengue
5. Filariasis

Ascaris-Causative agent- *Ascaris lumbricoides* lives in lumen of small intestine where it moves freely. The female length quantify 20-35 cm as well as it gives Twenty four thousand eggs per day and these eggs will infect the people. Eggs in small intestine are developed larvae. Figure 1 structure of filariasis.

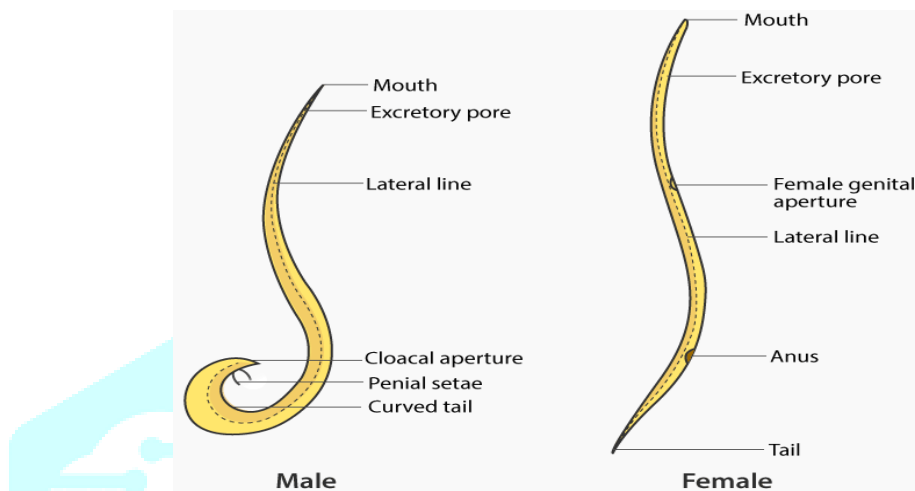


fig 1 : structure of filariasis worm

Cycle of worm- ^[3]

1. The larvae puncture the gut wall to liver.
2. And then to lung via blood.
3. They migrate bronchioles.
4. They are coughed to trachea and then swallowed by human host.

Treatment- Reduce contamination soil, Safe drinking water and food, Piperazine – citrate and phosphate are two available derivatives, Mebendazole- 100mg twice a day, Levamisole, Pyrantal. ^[2]

Dengue-Dengue is a viral infection (Arboviruses) transmitted to humans through the bite of infected mosquitoes. The first vehicle that transmit the disease are *Aedes aegypti* mosquitoes and, to a small range, *Aedes albopictus*. The virus fault for causing dengue is called dengue virus.

Causative agent- Arboviruses is transmitted through vector mosquitoes *Aedes aegypti* mosquitoes *Aedes albopictus*.

Cycle of Dengue-

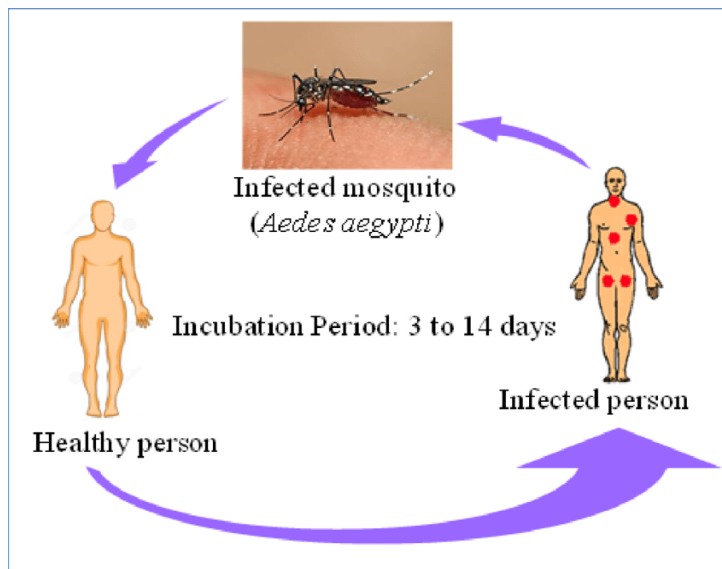


figure 2: cycle of dengue

Symptoms- Infection may be Asymptomatic or may following condition. Classical Dengue fever, Dengue hemorrhagic fever without shock, Dengue hemorrhagic fever with shock.

Filariasis- Parasites- Lymphatic Filariasis. Lymphatic filariasis, considered globally as a neglected tropical disease (NTD). Is a parasitic infection caused by microscopic, thread-like structure worm. The mature worms only live in the human lymph system. The lymph system maintains the body's fluid balance and fights infections. It is transferred by bites of infected mosquitoes.

Causative Agent- The commonly infective nematodes are Wuchereria Bancroft, Brugiamalayi and Brugiatimori. Mature worm live in lymphatic system of infected person. Microfilaria moves in blood .Whenever an infected mosquito bites peoples. The parasite is deposited near the site of infection. It passes through penetrate skin or many penetrate the skin on its own and reach lymphatic system. The incubation period is 8- 16 months.

Cycle of filariasis-

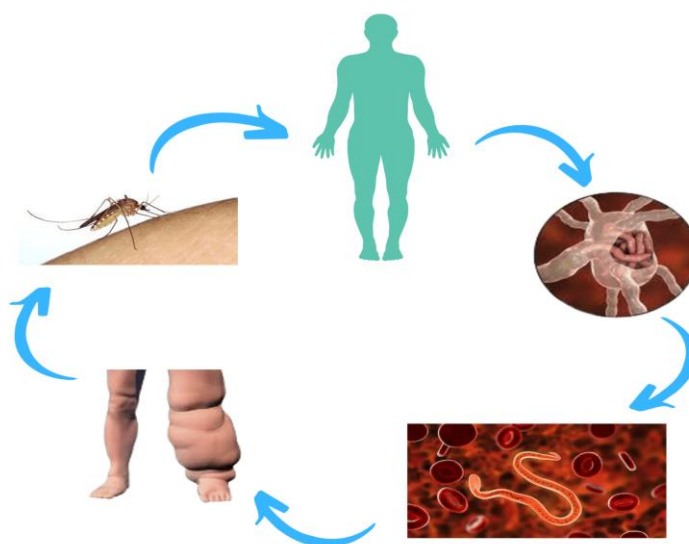


figure 3: cycle of filariasis

Treatment-Ivermectin.^[2]

Anti- Helminthic Drugs- Anthelmintic, any drug that acts against infections caused by parasitic worms (helminthes). There are amount of drug available in market to treatment of the worm infection. But in some of them the anthelmintic drugs are more dominant to cure the helminthic diseases.

Classification- based on chemical structure table 2 classification of anti-helminthes drugs.^[4]

table 2: classification of anti-helminthes drugs.

SR NO	CLASS DEPENDS ON CHEMICAL STRUCTURE	NAME OF DRUG
1	Benzimidazoles	Albendazole, Mebendazole, Thiabendazole.
2	Piperazines	Diethylcarbamazine Citrate (DEC), Piperazine Citrate
3	Heterocyclic	Oxamniquine, Praziquantal.
4	Macro cyclic lactone ring	Ivermectine, Avermectine.
5	VinylPyrimidine's	Pyrantel, Oxantel.
6	Amide	Niclosamide.

Drugs Action- Mebendazole- is a benzimidazole drug. It is a Broad Spectrum anthelmintic.

Structure-

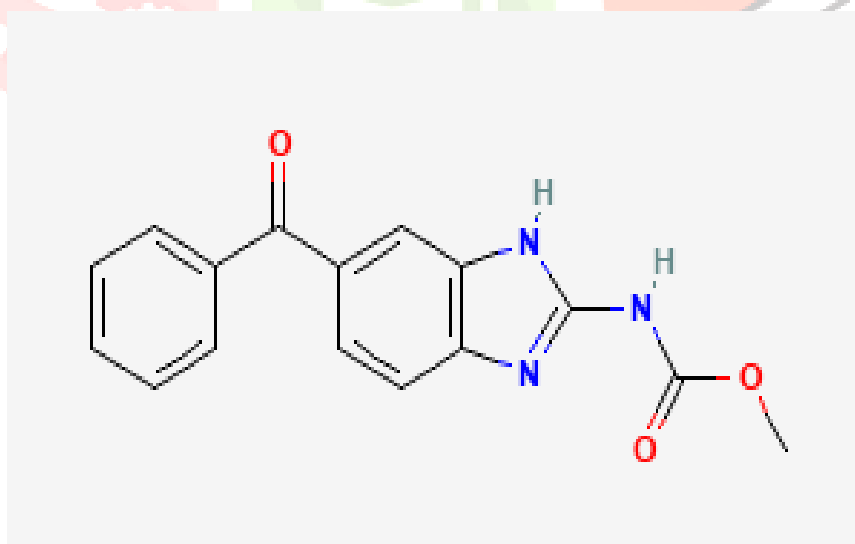


figure 4: structure of mebendazole

IUPAC Name- Methyl-(5-benzoyl-1H-benzimidazole-2-yl) carbamate.

MOA- it exerts an immobilizing and lethal action on worm. It is also block uptake of glucose by nematodes leading to glycogen depletion and reduce generation of ATP, required for survival resulting in the death of parasite.^[3]

Side effects- Headache, Diarrhea.

Diethylcarbamazine Citrate (DEC) – DEC is piperazine containing anthelmintic drug, which does not resemble other ant parasitic compounds. It is synthetic organic compound which is highly specific for several parasites and does not contain any toxic metallic element. It effective against filariasis and ascariasis. [5]

Structure-

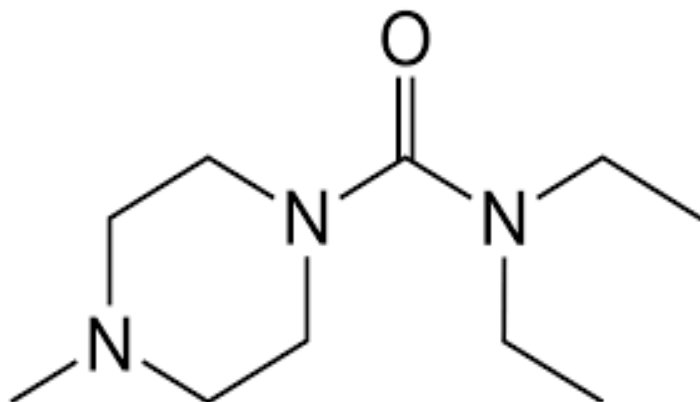


figure 5 diethylcarbamazine

IUPAC name- N, N-diethylpiperazine-1-carboxamide. [5]

MOA- DEC reduce of arachidonic acid metabolism in filarial microfilaria result in kill of microfilaria. [3]

Side effect- Rashes, dizziness, leukocytosis. [5]

III. A 5-OH substituted derivative of B1a-Ivermectine is potent Anthelmintic

Ivermectine- is a semi-synthetic derivative of avermectin which is introduced as anthelmintic in the 1980s by Merck contains a large macro cyclic lactone ring which is fermented product of micro-organism *Streptomyces avermitilis*. It is a powerful drug and conduct to development of ivermectin derivatives (ie.B1a and B1b). There are two types of Ivermectin derivatives seen for their substitution of methyl and ethyl group.

Structure of Ivermectin-

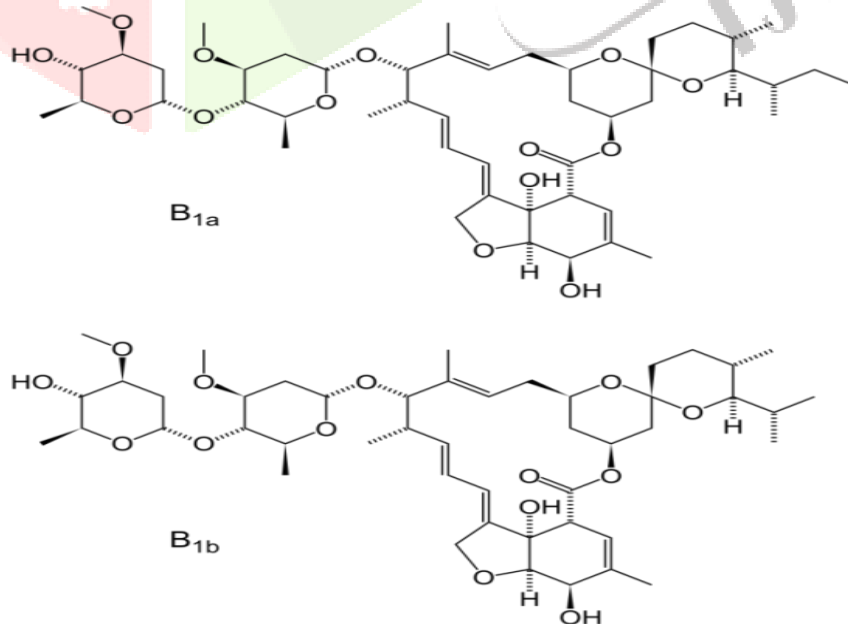


figure 6: structure of ivermectin b1a and b1b [1]

Chemical name- 22, 23-dihydroavermectin B1a + 22, 23-dihydroavermectin B1b.

Structure Activity Relationship^[5]

1. 4 O-substituted derivatives show biological activity.
2. 5 O-substituted derivatives have no biological activity.
3. Substituted of hydroxyl or methoxy group at 5-position is essential for ant parasitic activity.
4. The presence of two sugar moieties at position 13 is essential for biological activity.
5. Aliphatic nature of the ring having 5-OH/OMe is necessary for ant parasitic activity. If the ring is replaced by aromatic ring, then there is no activity

So that according to above Structure activity relationship the substituted of the hydroxyl or methoxy group at 5 position is essential for ant parasitic action. I can found that the B1a Ivermectin 5-OH group is replaced by OC₂H₅ group result can obtain B1aIvermectine substituted derivative is potent anthelmintic activity. The synthesis of compound is given by the following reaction.

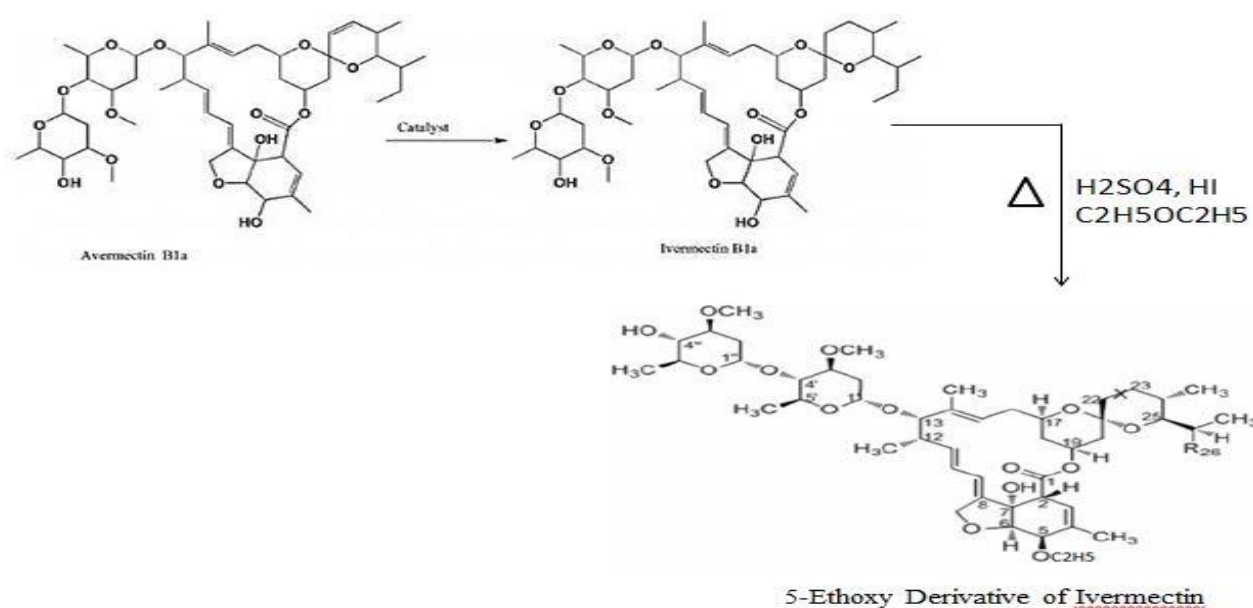
IV. SYNTHESIS OF B1A SUBSTITUTEDIVERMECTIN

1. Selective catalytic hydrogenation of the cis-22,23-double bond of the avermectins N1a and B1b. Catalyst used is Wilkinson's catalyst chlorotris (triphenylphosphine) rhodium (I) [RhCl(PPh₃)₃].

2. The first step is formation of IvermectinB1a. So we can add in this H₂SO₄. H₂SO₄ react with the ivermectine which results in removal of hydroxyl group and formation of unsaturated compounds.

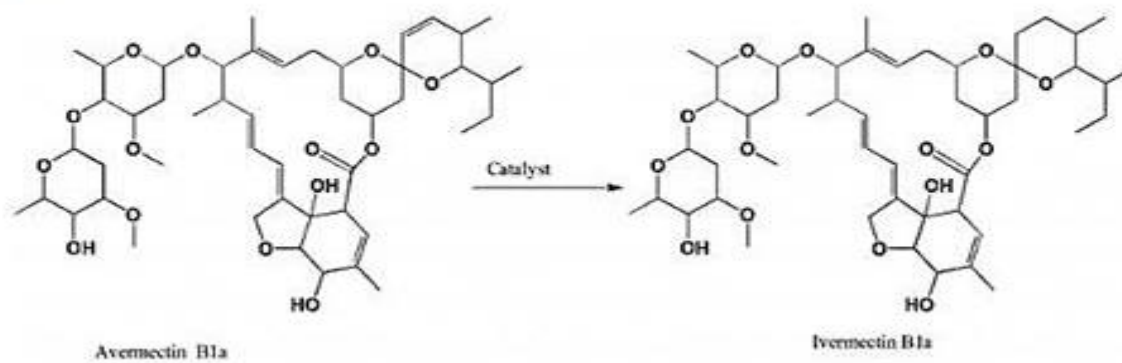
3. Then we can add HI in the Aromatic unsaturated compound, form the iodine substituted derivative and in last step I Diethyl Ether added with small amount of heat and synthesis of 5-Hydroxy derivative of Ivermectin.

V. REACTION

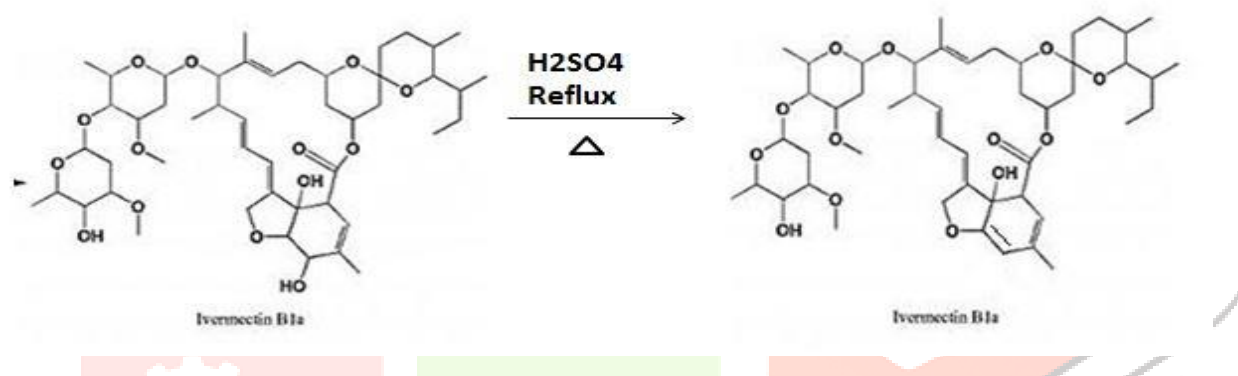


Mechanism

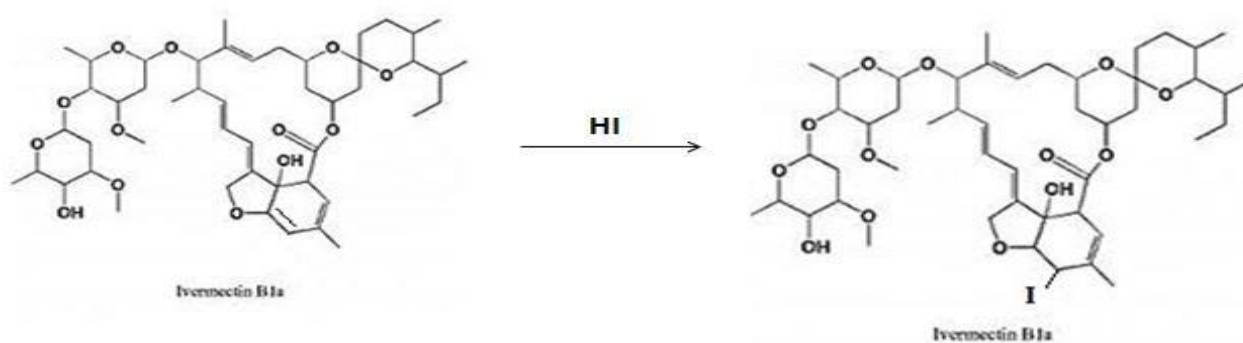
Step 1-



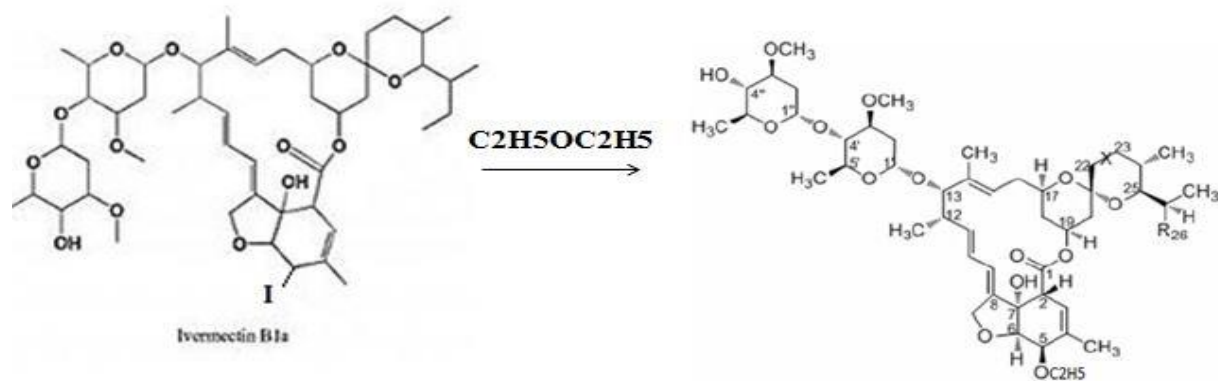
Step 2-



Step 3-



Step 4



So a new analogue is formed that is 5-Ethoxy Ivermectin. It has a powerful anti parasitic activity than the original Ivermectin.

VI. PHYSIOCHEMICAL PROPERTY OF 5-ETHOXY IVERMECTIN

Table 3 physical and chemical properties of 5-ethoxy ivermectin.^[6]

SR. NO.	PHYSICAL AND CHEMICAL PROPERTIES	
1	Molecular weight	900.1g/molar
2	Physical properties	White to yellowish white crystalline powder
3	Melting point	157°C
4	Solubility	0.005mg/ml in water
6	Presence of ring	Furan, pyran
7	Number of chiral centers	20

VII. MECHANISM OF ACTION

1. Ivermectin selectively binds with glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of microfilaria and increases the permeability of the cell membrane to chloride which results in hyper-polarization of the cell. This form to the paralysis of the parasite and eventually death.
2. It also action as agonist of the neurotransmitter GABA, reduce GABA-mediated central nervous central neurosynaptic neurons.
3. It also interrupt he intrauterine formation of micro-filariae and slowdown their release from uteri of gravid female worms.^[6]

Side Effect- Nausea, Muscle pain, Diarrhea, Dizziness, Headache, Joint pain. ^[6]

Uses- It is used as the Anthelmintic of different worm infection.

VIII. CONCLUSION

This review is based on the different types of derivatives of ivermectin and their action. Ivermectin is a drug that is used for treatment of parasitic diseases. Different types of drug used in market but ivermectin is potential drug which treat the parasitic diseases so it called as anthelmintics. Synthesized the 5-Ethoxy ivermectin derivatives will show the better action and less side effect than the ivermectin and other anthelmintics. The drug action is very specific and potential to treat disease.

IX. CONFLICTS OF INTEREST

The authors do not have any conflict of interest to declare.

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