Curr.Med. Chem.13, 3319 (2006)

Recent Developments in search of Antifilarial Agents

Rama Pati Tripathi,* Diksha Katiyar, Biswajit K Singh and Jyoti Pandey

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, 226001, India

*Address Correspondence to this author at the Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow-226001-India

Email: rpt_56@yahoo.com; Phone No. 91-522-2612412, FaxNo. 91-522-2623405

Abstract:

Filariasis, caused by spirunid nematodes, is one of the most prevalent diseases of tropical and subtropical countries and encompasses a number of different pathological conditions. The most common type of filariasis is a lymphatic filariasis caused by parasite that live in human lymph system. Like malaria it is also caused by mosquito biting. Life cycle, pathogenesis and diagnosis of filariasis have been briefly reviewed. Different strategies being applied to control this disease has been discussed with major emphasis on the mechanism merits and demerits of the existing drugs and the drugs under pipeline. New antifilarial prototypes discovered recently and the future perspective the desease have also been elucidated.

1.1. INTRODUCTION

Human existence has been afflicted with a remarkable number of parasites and during our relatively short history on Earth, we have acquired about 300 species of helminth worms and over 70 species of protozoa.[1] During recent times, the spread of human immunodeficiency virus (HIV) and AIDS and the resultant immunodepression caused by these diseases has led to surfacing of new opportunistic parasitic infections throughout the world.[2] Among the various parasitic diseases, the World Health Organization considers filariasis as one of the six potentially eradicable diseases and initiated a global plan for its elimination as a public health problem by the year 2020.[3] Filariasis, caused by spirunid nematodes, is one of the most prevalent diseases of tropical and subtropical countries and encompasses a number of different pathological conditions. The most common type of filariasis is a lymphatic filariasis caused by parasites that live in human lymph system. There are eight species of filariae which parasitise man along with many other species, which infect other vertebrates. In humans these reside in lymph glands, deep connective tissue, subcutaneous tissues or mesenteries. These spirunid species require an insect vector for successful completion of life cycle and transmission from one definitive host to another.[4, 5] Among all the species infecting man, *Wuchereria bancrofti* and *Onchocerca volvulus* having no animal reservoirs are difficult to study. Four of the species listed in Table-1 are primarily responsible for most of the cases of human filariasis: *Wuchereria bancrofti* and *Brugia malayi*, which are essentially lymphatic parasites, cause mainly lymphatic filariasis. The former is responsible for infection in 90 % of the filaria infected human while the latter accounts for 10 % cases. *Onchocerca volvulus* (sometimes called the African eye worm) and *Loa loa*, largely subcutaneous parasites, are responsible for onchocerciasis (river blindness) and loaisis respectively.

1.2. GLOBAL BURDEN OF DISEASE

Lymphatic filariasis, onchocerciasis and loiasis collectively afflicts around 200 million people worldwide and over 40 million of them are seriously incapacitated and disfigured. It has been estimated that about 1.1 billion people in more than 80 countries are exposed to infection risk.[6] The

Indian picture of filarial and its control has been recently elucidated by Pani's group.[7] One-third of the people infected with the disease live in India, one third are in Africa and most of the remainder is in South Asia, the Pacific and the Americas. The burden of this disease in humans and its impact on socioeconomic aspects has led to the identification of this disease as one of the priority areas of WHO[7]. Over 120 million people are affected by lymphatic filariasis, which is endemic in tropical and subtropical areas, and the prevalence of infection is continuing to increase. Presently, over 2.5 million people are exposed to the risk of infection with *B. malayi*, about 18 million people are infected with onchocerciasis, 40 million acquire loiasis and rests are affected by different species of parasitic filaroids.[7, 8] The global burden of the filariasis is increasing primarily due to the rapid and unplanned growth of cities, which creates numerous breeding sites for the mosquitoes that transmit the disease.[9, 10]

2. SYMPTOMS

Clinically, lymphatic filariasis is a spectral disease and there are three basic disease stages (a) asymptomatic (b) acute and (c) chronic. Asymptomatic microfilaraemia is often the most common manifestation of filariasis in many endemic populations and it is often regarded as a "non-disease" because the individuals concerned are unaware for decades of the presence of large numbers of microfilariae in their blood.[14] Most of the signs and symptoms of filariasis are caused as a consequence of the adult worms living in the lymph system. Tissue damage caused by the worms restricts the normal flow of lymph fluid resulting in swelling, scarring, and infections. The most common manifestation of acute filariasis[15] is adeno-lymphadenitis (ADL), which is characterized by intense lymphangitis, lymphadenitis and reddening of the overlying skin. In males there may be orchitis, epididymitis and acute transient hydrocoeles. The worst symptoms of the chronic disease[16] generally appear more often in male adults than in adult women. It includes persistent lymphoedema of arms and legs, hydrocoel, elephantiasis of genital organs and chyluria (milky urine). Although, mortality is not associated with filaria, yet morbidity due to above-mentioned clinical manifestations is highly significant and major cause of socioeconomic problems.[17]Development of tropical pulmonary eosinophilia characterized by nocturnal cough and wheezing, low grade fever, and adenopathy has also been observed in few cases.[18a] In addition, even more common than the overt abnormalities is hidden, internal damage to the kidneys[18b] and lymphatic system caused by the filariae.[18c]

In contrast to *W. bancrofti* and *B. malayi*, it is the microfilariae of *O. volvulus*, rather than the adult worms, which are the principal cause of the pathology of onchocerciasis. Migration of these results in (a) onchocercal dermatitis, (b) onchocercomata (nodules) and (c) visual impairments and blindness.[12] Loaisis is mainly associated with temporary localized edema (Calabar swellings), episodic subconjunctival migration of the adult worm, dermatitis and fatigue.[13, 19]

3. LIFE CYCLE AND PATHOGENESIS

Different species of the Culex, Anopheles, Aedes and Mansonia genera of mosquitoes are vectors of *W. bancrofti* filariasis, depending on geographical distribution. The infective third stage larvae (L_3) are discharged to the human host during bite by an infected mosquito onto the skin and penetrate into the blood capillaries. through the bite wound during the short period that a mosquito is biting. Within nine months they become sexually mature and commonly reside in the lymphatics. The female worms measure 80 to 100 mm in length and 0.24 to 0.30 mm in diameter, while the shorter males measure about 40 mm by 0.1 mm. The mature females discharge microfilariae (mf) into the pleural cavity, measuring 244 to 296 μm by 7.5 to 10 μm, which are sheathed and have nocturnal periodicity, except the South Pacific microfilariae, which have the absence of marked periodicity. These are essentially pre-larval stages, which will not undergo further development until taken into the haemocoel of the intermediate host. The microfilariae migrate into lymph and blood channels moving actively through lymph and blood. On ingestion by the mosquito host the sheath is lost and mf migrate rapidly to the thoracic muscles where they develop into first-stage larvae (L_1) and subsequently into L_3. The infective L_3 migrate through the hemocoel to the mosquito's proboscis and can infect another human during the mosquito bite.[11, 20] The life cycle of *Brugia malayi*, which also parasitise the lymph nodes and lymphatics, resembles with that of *W. Bancrofti* and the adults of the two species are indistinguishable. The major vectors belong to the subgenus *Mansonia* and a few sp. of Anopheles. The life cycle of *O. volvulus* is similar to that of *W. bancrofti*, except that the intermediate hosts are various species of blackfies and buffalo flies of the genus *Simulium*.

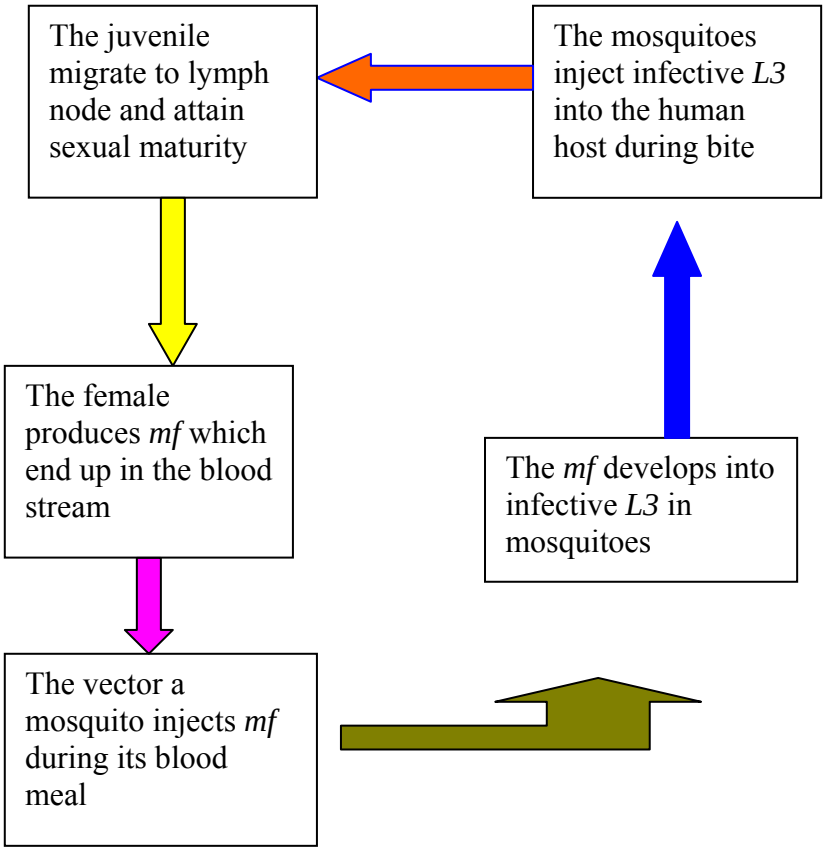


Figure 1 Life cycle of Filarial parasite (W. bancrfoti and B. malayi)

4. DIAGNOSIS

Although various techniques for identification of filarial parasite in blood are known today yet the only unequivocal means of ascertaining active filarial infection is by demonstrating parasites in host tissue. In the case of lymphatic filariasis and loaisis this is most commonly achieved by detection of microfilariae in the blood stream by microscopic examination of thick smear.[21, 22] However, in most parts of the world, the parasites have a "nocturnal periodicity" that restricts their appearance in the blood to only the hours around midnight. Membrane filtration of the venous blood is usually a more sensitive technique but it still poses inconvenience to communities where the disease has a nocturnal periodicity.[23] Clinical diagnosis is also routinely used but it is most

often insensitive, nonspecific and cannot distinguish between active and past infection. In the past few years, new methods for the diagnosis of filariasis, which are simple, more sensitive and cost effective, have been developed. Polymerize chain reaction (PCR) methods have been successfully used in the detection of parasite DNA in the blood.[24] A combination of PCR-ELISA method for detection of filarial DNA has been devised by Fisher et al.[25] The *W. bancrofti* antigen test based on the monoclonal antibody Og4C3, an antigen-capture ELISA (Enzyme linked immunosorbent assay) is used in field studies.[26] The other commercially available antigen test, the immuno-chromatographic technique (ICT) rapid card test,[27] using specific monoclonal and polyclonal antibodies, is now widely accepted as the tool of choice for survey work because of its simplicity and its ability to provide "on the spot" data. Recently, ultrasonography using a 7.5 or 10 MHz probe has helped to locate and visualize the movements of living adult filarial worms, the 'filaria dance sign' of W. bancrofti in the scrotal lymphatics of asymptomatic males with microfilaraemia.[28a] Lymphatic dilatation, dermal back flow and obstruction can be directly demonstrated in the oedematous limbs by lymphoscintigraphy which use radionuclide.[28b] With this and other new diagnostic tools,[30] it is now possible both to improve our understanding of the infection site and to monitor more easily the effectiveness of treatment and control programs.

5. DRUG DEVELOPMENT AGAINST FILARIASIS

Only a limited number of drugs including diethylcarbamazine, ivermectin and albendazole are known today and efforts are on to develop new drugs. However, efforts are being made indifferent parts of the world to develop new antifilarial agents based on different biochemical targets and the same has been reviewed below in short.

5.1. Target sites for drug development

Recent developments in the study of the basic physiology and biochemistry of filarial parasite have allowed the identification of novel targets for chemotherapy. Very recently Gupta et. al.[29] have reviewed different biochemical targets including carbohydrate, lipid, aminoacid and protein metabolisms, nucleic acid metabolism, folate metabolism, biogenic and polyamines metabolism, glutathione metabolism, retinol binding protein metabolism, the microtubular system, filarial receptors and channels and immunomodulation which have possibility to be exploited in drug design and the details can be found there. Here we are concerned only those targets which are

validated to potent antifilarials of clinical use. These include nicotinic acetylcholine receptor, γ-amino butyric acid (GABA) receptor channel, glutamate-gated chloride channel, β-tubulin, arachidonic acid metabolism, antioxidant defence system and DNA topoisomerases. It is quite possible that the target sites present in the parasite may be more or less similar to the host and therefore in selecting the targets for antihelmintic agents it is essential to select targets, which are absent in the host and specific to parasite.

5.1.1. Nicotinic acetylcholine receptors[31, 32]

Nematode possesses both synaptic and extrasynaptic nicotinic acetylcholine receptors in somatic muscle cell. It is evidenced that application of acetylcholine and anthelmintics, levamisole, pyrantel and morantal resulted in the polarization and increase in input conductance of the muscle membrane to Na^+ and K^+. It has been established that the nicotinic anthelmintics have an action on a receptor with similar but not identical properties to those in mammals and vertebrates. Based on definite studies it is now clear that there is some pharmacological difference between the nicotinic receptors of nematodes to those of their hosts, since levamisole is a selective agent producing depolarization and spastic paralysis of the nematode without a significant action on the host muscle. These anthelmintics are thought to act as a channel blocker.

5.1.2 GABA receptor channel[33]

γ-Amino butyric acid (GABA) receptors involved in many biological functions of the organism play very important role in anthelmintics too. Piperazine series of compounds showing anthelmintic activities act as simple GABA agonist and gates open GABA receptors on the somatic muscles of the nematodes. These compounds increase the Cl^- conductance of the muscle membrane leading to an increase in the membrane potential resulting in relaxation of the body muscles and flaccid paralysis.

5.1.3 Glutamate-gated Cl^- channel[34, 35]

The anthelmintics belonging to avermectins increase the Cl^- permeability of nerve and muscle membrane of the inveretebrates but the identity of the target ion channel has been controversial. It has been suggested that they act on a glutamate-gated Cl (GluCl) channel, which is a pentomer like that of nicotinic receptor. Different studies have concluded that ivermectins affect the glutamate receptors that gate chloride channels and the latter is potentiated by drugs.

5.1.4. β-Tubulins[36, 37]

Microtubules, serving variety of intracellular functions including transport of cytoplasmic secretary vesicles, are formed in a dynamic process by combination of two 450 amino acid proteins known as α-tubulin and β-tubulin. The formation of microtubule basically involves polymerization of tubulin at one end (positive pole) and the depolymerization at the other end (the negative pole) and this process is influenced by a number of factors including GTP, Mg and an increase in the temperature. Microtubule synthesis may be prevented by chemicals, which bind the positive pole, (the leading edge) of polymerization called as capping. The capping can be achieved by several alkaloids including colchicines, vinblastin, vincristine or the benzimidazoles, which bind the β-tubulin molecules. Benzimidazole anthelmintics compete for the binding site on β-tubulin with colchicines, which is known to block cell division in metaphase.

5.1.5. Arachidonic Acid Metabolism[38-40]

Arachidonic acid, a substrate for the formation of eicosanoids by the enzymatic oxygenase, is a 20 carbon polysaturated fatty acid derived from dietary essential fatty acids. Eicosanoids, which include prostaglandins and leukotrienes, exhibit diverse range of potent biological actions, which include effects on platelet aggregation, vasodialation, leukocyte inflammatory and immune functions and cellular adhesion. Microfilariae have the capacity to utilize host polyunsaturated fatty acids to generate specific eicosanoids, which are involved in mediatry interactions with adjacent cells. The production of specific eicosanoids with selective effects on host cells may be important in the survival and pathogenecity of the filarial parasites. The metabolism of arachidonic acid in filarial worms has been used as a target for the treatment and control of lymphatic filariasis.

5.1.6. Antioxidant defense system[41-46]

All filariae posses potent enzymatic and non-enzymatic defence mechanisms against the oxidative stress and other toxic substances generated in the biosystem. Oxidative stress is an inevitable result of aerobic metabolism and consists of reactive oxygen intermediates, superoxide anion radical ($O_2^{\cdot -}$), hydrogen peroxide H_2O_2, hydroxyl radical ($^{\cdot}OH$), alkoxyl radicals ($RO^{\cdot}$), peroxyl radicals ($ROO^{\cdot}$), nitric oxide ($NO^{\cdot}$) and other nitrogen-based intermediates. Role of various oxidants in damaging membrane proteins, lipids and nucleic acid is sufficient to kill cells and even the whole

organism. The main anti-oxidant enzymes in the parasite include superoxide dismutase (SOD), glutathione (GSH) and peroxiredoxins. Superoxide dismutases (SODs) protect cells by catalysing the dismutation of $O_2.^-$ to H_2O_2 and ground-state oxygen and also by preventing formation of $ONOO^-$ and O_2^-. These also inhibit lipid peroxidation and formation of peroxynitrite. Peroxiredoxins play a major role in peroxide metabolism in filariae and provides protection against by-products of aerobic metabolism and protect DNA from nicking in a metal-catalysed oxidation system. Glutathione, a small tripeptide (L-γ-glutamyl-cysteinylglycine), is an important part of the antioxidant system of filarial worms and protect them from attack by reactive oxygen species (ROS). It also facilitates the detoxification of electrophilic toxic compounds, xenobiotic substances and other superoxides. Moreover, it is also responsible for the maintenance of intracellular thiol redox status and thus for the function of many biological processes within the cell. The non-enzymatic anti-oxidant defence system including ascorbate, α-tocopherol, albumin and ubiquinols, are effective scavenger of hypohalous acids hydroperoxides. Thus different enzymes and molecules involved in the antioxidant defence mechanism of the filarial parasite can act as a decisive and potential target for antifilarial drug development.

5.1.7. Filarial DNA and DNA Topoisomerases

Filarial parasites contain DNA, which is rich in AT content and exhibits low stability, polyamines like putrescine, spermidine and spermine, interact with nucleic acid and play crucial role in stabilization, precipitation (aggregation, condensation) and B to Z transition of nuleic acid, with a different mode of action and metabolism from the human host, thus offering potential target for chemotherapeutics. The unusual features of DNA in filarial parasites and destabilization of DNA by some antifilarials together with a typical polyamine metabolism are likely to be potential chemotherapeutic targets in the design of antifilarial drugs.[47]

DNA Topoisomerases II are enzymes that alter the topology of DNA and have been the focus of considerable study in the areas of molecular and cellular biology and also experimental chemotherapy. These are involved in many reactions including ATP dependent negative supercoiling, ATP independent relaxation of negatively supercoiled DNA, formation and resolution of catenated DNA and DNA dependent ATP hydrolysis.[48] The coumarin group of antibiotics acts by inhibiting DNA gyrase. The drugs bind to the B subunit of gyrase and inhibit DNA supercoiling by blocking the ATPase activity. The mode of inhibition of the gyrase ATPase reaction by

coumarins is unlikely to be simple competitive inhibition and the drugs may act by stabilizing a conformation of the enzyme with low affinity for ATP. [49]

5.2. Filarial Genomics

WHO and United Nations Development Program//World Bank/WHO special program for research and training in tropical Diseases (TDR) initiated a program in 1994 to study the genomes of five species of parasites causing filariasis. The long-term goal of projects is to understand important biological problems such as parasite drug resistance, pathogenesis, and virulence and to assist in the identification of new targets for chemotherapy and vaccines.[50] As a new approach for understanding the biology and the biochemistry of filarial parasites, genome projects are directed at the identification, cloning and sequencing of all the genes of organisms. For constructing the necessary cDNA and genomic libraries, to study filarial genomes, parasites of various life cycle stages were collected from many parts of the world. Now, 26,215 ESTs (Expand expressed sequence tags sequencing) containing more than 10 million base pairs of *B. malayi* sequence data, 14,974 ESTs for *O. volvulus* and more than 6,000 ESTs for *W. bancrofti* are available. In total this represents about 20 million base pairs of expressed filarial parasite DNA sequence.[51] Moreover, the complete sequence of the mitochondrial genomes[52] for filarial parasites (*O. volvulus* and *B.malayi*) is also carried out providing additional targets for biological study and potential chemotherapy. Recently, the development of a transgenic technique for introducing DNA[53] and RNA*i* technique for introducing RNA[54] into the cells of parasitic organisms open up the possibility for studying gene function and for the identification of vaccine candidates and drug targets.

5.3. The endosymbiont bacteria

Wolbachia is a group of intracellular bacteria, discovered in the 1970's and belong to the order Rickettsiales.[55] These are endosymbiont of filarial nematodes and play an important role in the development, viability and fertility of their host. Symbiont bacteria may be implicated in the pathogenesis of filarial pathology and inflammatory responses of the filarial parasites are probably due to the release of bacteria and their products either on death of the parasite or through a variety of secretary and excretory mechanisms.[56] Several studies have shown that killing the *Wolbachia* bacteria results in reduced fecundity and often death of the filarial parasites. Many antibiotics tetracycline, doxycycline, rifampicin, novobiocin and their combination are known to be effective in the treatment of human filariasis via targeting endobacteria.[57] Since this intracellular bacterium

contributes to the normal functioning of the filarial parasite, thus it provides a novel target for antibiotic based chemotherapy and vaccination interventions.

6. FILARIASIS CONTROL

There are several approaches to curtail vector borne filarial diseases: vector control, breaking of vector-host contact by use of repellents and bed nets, vaccination and chemotherapy.

6.1. Vector Control

Vector control has played an effective supporting role for filariasis control in certain local programs and reduction of vector density can be an important contributor to achieving long-term sustainability of transmission interruption.[58] However, filariasis control program should not be based upon vector reduction alone, rather vector control should be implemented whenever feasible as a complementary tool to filariasis control program based primarily on drug administration. Traditional vector control methods include: killing of mosquitoes or "adulticiding", interrupting transmission of disease by mosquito vector by mosquito repellants, mosquito nets for sleeping and also to avoid the habitat when the vector is at its peak biting times. Certain improved techniques for enhancing the effectiveness of vector control are now available, including (1) Biocides: especially *Bacillus sphaericus* (a toxin producing bacterium) to control *Culex quinquefasciatus* (2) Polystyrene beads: to limit breeding of culicine vectors in specific urban situations with enclosed breeding sites (3) Indoor spraying of long lasting residually active pyrethroids: especially for adult stage culex and mansonia and (4) community participation in integrated vector management. Vector control can be very successful when malaria and filariasis have common vectors.[59] However, vector control takes a long time to become effective and is very labour intensive and costly and the development of insecticide resistance makes it less effective.

6.2. Insecticide-treated bed nets

Insecticide-treated bed nets have the potential to reduce filariasis transmission[60] but they are of only limited effectiveness because there are a large number of mosquito species that transmit filariasis and some of these bites during the time of when people are not under bed nets.

6.3. Vaccines

The current three anti-filarial drugs, DEC, ivermectin and albendazole, being used are not totally curative and numerous rounds of mass treatment will be necessary to reduce the levels of infection

below those necessary to sustain transmission. Thus, efforts are needed to generate a vaccine that might be a cost-effective either to enhance the effectiveness of drugs in eliminating LF and to help to prevent its recrudescence or both.[61] Despite some promising research, a vaccine for any of the filarial parasite is not yet a reality.[62] Recently some progress has been made in this area with cloned filarial antigens, a recombinant chitinase and a protective epitome SXP1 (an antigen found in multiple worm stages showing promise as vaccine candidates).[63] A serine protease inhibitor expressed by *B. malayi* microfilariae that inhibits neutrophil serine protease and aids the parasite to evade the immune system, may be a target for vaccine development.[64] Over the past decade there has been dramatic improvement in our understanding of the mechanisms that lead to develop new vaccine candidates against filarial L3 and *mf* stages. Out of several factors, the most important factor in vaccine development are development of animal models and molecular biology along with the advent of new technologies such as RNA interference (RNA*i*), protein three-dimensional imaging and novel methods of gene delivery.[65]

6.4. Chemotherapy

The two general strategies to control filarial infections using chemotherapy include selective and mass treatment. In selective therapy individuals are examined for the presence of disease and the infected individuals are treated. However, this approach is inefficient and is associated with major problems. If *mf* is used as the indicator of infection many infected people will be overlooked, as most of them are amicrofilaraemic. People with very low microfilarial densities may not be detected and it has been shown that such people are capable of infecting mosquitoes and causing a resurgence of disease.[66] The use of antigen testing will overcome these problems but it still suffers with the logistical problem of screening all members of the community. If selective chemotherapy is used the lost infections are balanced by new infections to produce a dynamic equilibrium and their needs to be continual reassessment of the filarial status of the community to identify the newly infected persons.[67] Mass treatment aims to treat all members of the endemic community at the same time and will therefore treat pre-patent as well as patent infections. In other words the community becomes the focus of the control program rather than the individual.[68]

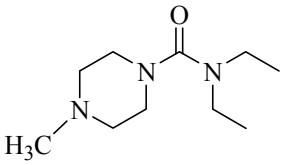
In the first half of the 20th century, many drugs were tested for activity against filarial parasites. For the most part, drug efficacy was low and toxicity was unacceptably high. Originally antimony and arsenic based drugs and naphthalene sulfonic acid (Suramin) were used to treat filariasis but with limited success.[69] Suramin has been shown to be moderately active against adult *W. bancrofti* and

B. phahangi[70] but it has no effect on microfilariae and therefore it does not interrupt the transmission cycle in the short term. It is also relatively more toxic than other antifilarial drugs and is not widely used today.[71] Levamisole has been shown to limit activity against filarial parasites.[72] In recent times identification of ivermectin and albendazole as new, effective anti-filarial agents and the discovery of new virtues for an old anti-filarial drug, DEC (i.e., its single-dose efficacy and macrofilaricidal action) and subsequent creation of the Global Program to Eliminate LF and other chemotherapy programs,[73, 74] are the major advances in filarial control ever made. Besides the above mentioned drugs, there are few other drugs, which have been marketed and all these are described below.

6.4.1. Diethylcarbamazine (DEC)

Since its discovery in 1947 by Hewitt et al.,[75] diethylcarbamizine, the piperazine derivative, (DEC, proprietary names: Hetrazan, Banocide and Notezine) has been, and still being most widely used drug for the treatment of lymphatic filariasis.[69, 76, 77] It is clinically used as the dihydrogen citrate salt and is given orally. It reaches all parts of the body within 25 minutes after its intake. Accurate blood levels of DEC can be determined by ELISA.[78] The plasma half-life varies from 6.1 to 8.1 hours. Excretion of the drug is mainly renal and the blood concentration reaches zero within 48 hours. DEC is a highly effective microfilaricidal drug.[79] However, varying degree of macrofilaricidal activity at different doses has also been reported.[76, 80, 81] The standard DEC treatment regime is 6 mg/Kg per day over a 10 to 20 day period.[69, 82] This is suitable only for treating isolated cases but not for community-wide mass treatment programs.[83] Other regimes for mass treatment are: monthly doses, 6 monthly doses and annual doses. Common cooking salt medicated with DEC in concentrations ranging from 0.1% to 0.6 % has been effectively used in mass treatment programs for lymphatic filariasis.[82, 84] Current practice in mass drug treatment with DEC is a single annual dose of 300 mg of DEC for adults and 150 mg for children (often combined with Ivermectin, and sometimes with Albendazole also).[85, 86] It can be utilized in most of the control programs, but cannot yet be recommended in areas where there is co-existing onchocerciasis or loiasis.[87] The above dose of 6 mg/Kg is associated with few side effects such as drowsiness, nausea, and gastrointestinal upset and these are observed more frequent with increase in dosage of the drug. Adverse reactions that are triggered by DEC in persons with filarial infections can be either localised (associated with death of the adult worm) or systematic (associated with death of the microfilariae).[88] The mechanism of action of DEC is still not well

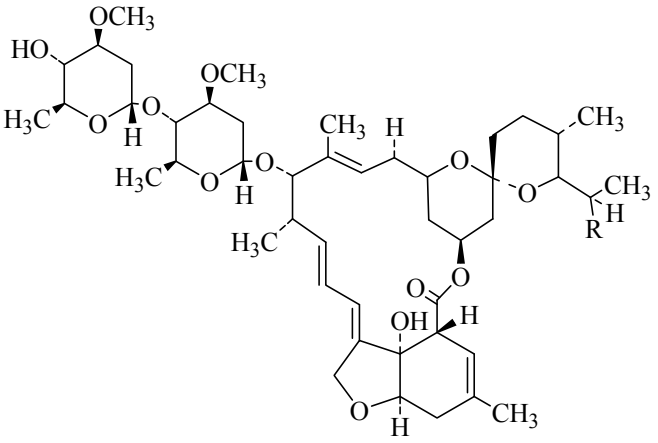
known. However, a reasonable explanation for its action is that it alters the metabolism of arachidonic acids in the host endothelial cells and microfilariae. As a result of this, there is constriction of the blood vessels and aggregation of the host granulocytes and host platelets. Thus it appears that DEC activates an innate immune response rather than an adaptive response. [89]



Diethylcarbamazine

6.4.2. Ivermectin

Ivermectin, also known as mectizan, a macrolide antibiotic, is a semisynthetic derivative of avermectin. It has been used very successfully for the treatment of oncocerciasis for a number of years.[90, 91] It is active against skin dwelling first stage larvae (microfilariae) of *O. volvulus* at exceedingly low doses of 150 μg/kg body weight. A single annual dose of 400 μg /kg, either alone or in combination with 6 μg /kg of DEC, has been proved to be very effective in producing long-term suppression of microfilaraemia in lymphatic filariasis in a number of countries. The single dose ivermectin regimen appears equivalent to single dose DEC regimens in efficacy, safety and tolerance and in addition it can be used safely in areas where coexistence of onchocerciasis or loiasis is common. Like DEC, it is also associated with several adverse effects.[92] Although macrofilaricidal effect of ivermectin has been proposed but it is clear now from recent ultrasound studies that the adult worms are not killed even at total doses of 4800 μg/kg over a period of 6 months.[80b, 81, 93] Recently serious side effects, mainly *Lao loa* encephalopathy, following ivermectin treatment for control of onchocerciasis in areas co-endemic for loaisis has been reported.[94, 95] The antiparasitic mechanism of ivermectin is through selective and high affinity binding of the drug to the glutamate-gated chloride ion channels in invertebrate nerve and muscle cells. It increases the permeability of the cell membrane to chloride ions, resulting in hyperpolarization of nerve or muscle cells, causing paralysis and/or death of the parasite. The drug is also observed to effect other ligand-gated chloride channels, particularly those gated by gamma-aminobutyric acid. However, it is still not certain why ivermectin shows activity only against *mf* and not adult worms.[90b]

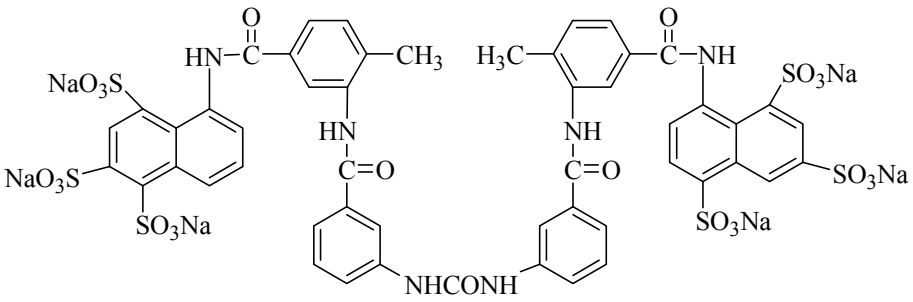


Component B_{1a}, R = C_2H_5 **Component B_{1a} R = CH_3**

Ivermectin

6.4.3. Suramin

Suramin (antrypol) was initially introduced as antitrypanosomiasis drug in 1920's and subsequently it was found to be an effective antifilarial also. It is the only macrofilaricide currently available for use against *W. bancrofti*, *Onchocerca volvulus* and other filarial parasites. However, when administered intravenously over a period of several weeks, it is also effective against microfilariae.[96] It is however, one of the most toxic substances used in clinical medicine and should always be given under medical supervision in a hospital.[97] Many adverse reactions are associated with suramin treatment and some of them occur rarely but are very fatal.[98,99]

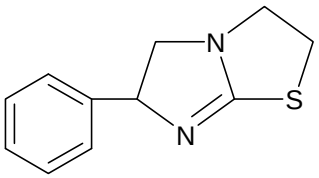


Suramin

6.4.4. Levamisole

It was first introduced in 1965 and exhibits potent activity against intestinal helminthes but has not been found to be very active against filarial parasites. However, its ability to kill microfilariae of *W.*

Bancrofti, *B. malayi* and *O. volvulus* to some extent has been reported.[96b] It acts as a non-humoral immunostimulant in immunosupressed individuals. However, the mechanism of this stimulation is unknown.[71, 100, 101]



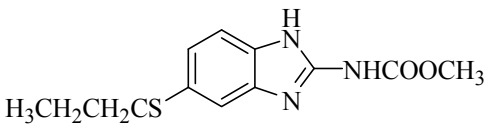
Levamisole

6.4.5. Benzimidazole

Benzimidazoles have offered major advances in the therapy and prophylaxis of gastrointestinal helminth infections since a long time in clinical medicine. Among benzimidazoles, albendazole and mebendazole have been widely used in human filarial infections. The primary target for benzimidazoles is tubulin and the drugs are observed to have a higher affinity for parasite tubulin than for that of the host.[102] Blockage of tubulin polymerization and microtubule formation by the drug inhibits mitosis, and therefore embryogenesis and egg hatching. It is very likely that these exert an effect on adult filariae in this manner. Benzimidazoles are known to be teratogenic and embryotoxic therefore they should not be administered during pregnancy. [103] Few of such benzimidazoles are briefly described below.

(i) Albendazole

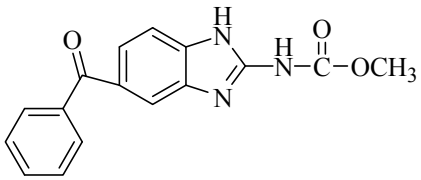
Albendazole is a broad spectrum anthelmintic firstly introduced in 1979 and has high potential in tackling enteric helminthiases but it has only recently been assessed as an anti-filarial and found to be more effective when combined with DEC or Ivermectin. The problem of adverse reactions with albendazole is no better or worse than with DEC or Ivermectin.[104] The macrofilaricidal activity of albendazole for the treatment of individual patients is reported as one of the most important breakthrough in filarial chemotherapy.[105]



Al bendazole

(ii) Mebendazole

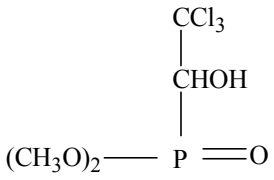
Mebendazole, a broad spectrum anthelmintic, was first introduced in 1972 as a drug. It prevents the development of the embryos in onchocerciasis and when given in conjunction with levamisole both microfilaricidal and embryostatic effects can be achieved.[101, 106] Besides, its action on tubulin, the drug also affects glucose uptake by helminth that in turn follows an enhanced utilization of endogenous glycogen. It causes diminished ATP synthesis and turnover of adenine nucleotide also.[107, 108]



Mebendazole

6.4.6. Metrifonate

Metrifonate (trichlorphon) is basically an organophosphorus insecticide and it is also effective in treating nematode infections. It acts by inhibiting cholinesterases and thus paralysising the worm. It has been used clinically in the treatment of *W. bancrofti* and *O. volvulus* infections and is an effective microfilaricide.[96b, 109] Metrifonate therapy is also associated with side effects and some are mild but severe side effects also arise in some cases.[110, 111]



Metrifonate

6.4.7. Combination therapy

Several recent studies have explored the effectiveness of co-administration of two or more than two drugs for filarial chemotherapy. A combination of DEC (6 μg/kg) and ivermectin (400 μg/kg) has been shown to be very effective in providing rapid and long-term clearance of microfilariae. When given sequentially or in combination, DEC and ivermectin tend to produce more prolonged

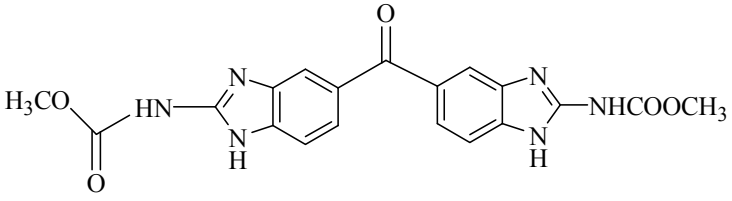
suppression of microfilaraemia than either drug alone.[112, 113] Another study showed that a combination of albendazole (400 mg) and ivermectin (200-400 μg/kg) gave the more microfilaricidal effect than either drug alone.[104b] In addition to the significant microfilaricidal activity induced by these drug combinations, macrofilaricidal effects of albendazole, DEC and ivermectin combination was also studied. Although all sorts of combinations were well tolerated and effective macrofilaricide[114, 115] but the single dose combination of albendazole and DEC was the best regimen to decrease antigen levels (presumably reflecting the presence of viable adult worms), though antigen clearance was not achieved. However, a combination of 600 mg of albendazole with 6 mg/kg of DEC was found to be most effective and decreased the filarial antigen levels by 77 % in 15 months after therapy.[114]

7. THE SEARCH FOR NEW ANTIFILARIAL AGENT

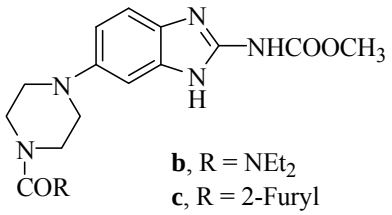
The present antifilarials like diethylcarbamazine (DEC), ivermectin and albendazole are mainly targeted at microfilaria and have low macrofilaricidal activity.[8c, 115-117] Many of the adult parasite, therefore survive after the chemotherapy and lead to reappearance of microfilaria several months after treatment. Further, the adverse reactions of present drugs and the current report of resistance development necessitates the development of new antifilarial drugs that have macrofilaricidal efficacy and show total and long lasting suppression of embryo production to complement currently available microfilaricides. Few of the recently discovered compounds possessing antifilarial activity are given below

7.1. Benzimidazole derivatives

Few, new benzimidazoles have been discovered recently possessing potent antifilarial activity. A compound 2,2'-(dicarbomethoxyamino)-5,5'-dibenzimidazolyl ketone (**a**)[118, 119] and two other benzimidazole derivatives methyl 5(6)-(4-substituted piperazin-1-yl) benzimidazole-2-carbamates (**b** and **c**) have shown potent microfilaricidal and adultiucidal activity.[120]

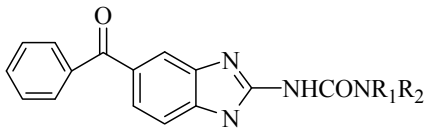


a

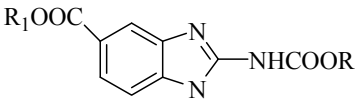


b, R = NEt_2
c, R = 2-Furyl

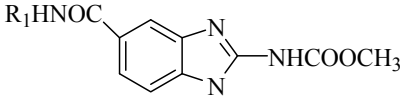
Several compounds with substituents at 2-amino nitrogen and C-5 of the benzene ring have been synthesized and evaluated for antifilarial efficacy. Out of these 1-(5-benzoylbenzimidazol-2-yl)-3,3-dimethyl urea (**d**) showed 100 % macrofilaricidal activity against both *Brugia. pahangi* and *Litomosoides carinii* and 87 % microfilaricidal activity against *L.carinii*.[121] Some of the compounds of series alkyl 5-(alkoxycarbonyl)-1H-benzimidazole-2-carbamates (**e**) and methyl 5-carbamoyl-1H-benzimidazole-2-carbamates (**f**) have also been reported to be active *in vivo* against adult worms of *B. pahangi*, *L. carinii* and *Acanthocheilonema viteae* in experimentally infected jirds.[122]



d



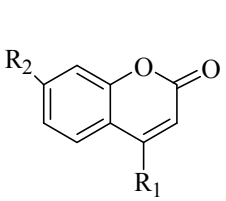
e



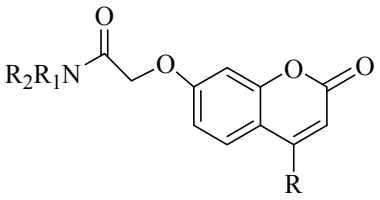
f

7.2. Coumarin derivatives

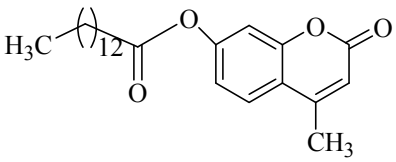
Benzopyrone (coumarin) has been reported to reduce lymphodema in filarial patients and other types of inflammation, apart from its effect on adult parasites, when administered alone or in combination with DEC.[123] In an attempt to develop such derivatives some compounds from our laboratory earlier showed activity on adult filarial parasites of rodent species.[124] A number of 2*H*-1-benzopyran-2-one and related compounds (**a**) synthesized in our group have shown significant effects on macrofilariae.[125, 126] A series of 7-*O*-acetamidyl-4-alkyl-2*H*-1-benzopyran-2-ones (**b**) prepared by us inhibited filarial DNA topoisomerase under *in vivo* condition in *Setaria cervi* and *in vitro* against *Brugia malayi*.[127] One of the compounds with hexadecyl chain at *N*- was most effective at 20 µg/reaction mixture concentration inhibiting topo-II activity by 80 %. Another compound 4-methyl-7-(tetradecanoyl)-2*H*-1-benzopyran-2-one (**c**) showed promising microfilaricidal, adulticidal activity and also caused sterilization of female worms. [128]



a



b

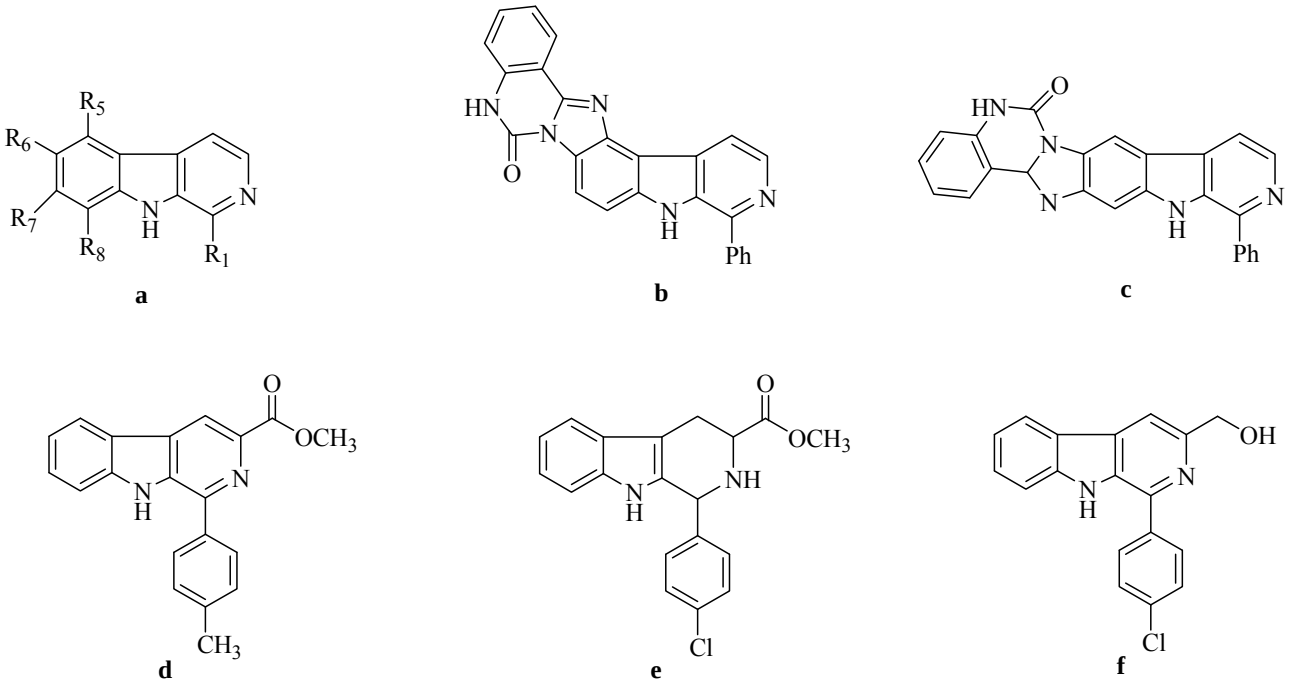


c

Coumarin Derivatives

7.3. 9*H*-Pyrido[3,4-*b*] indoles

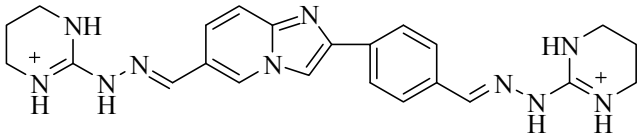
The 9*H*-pyrido[3,4-*b*]indole (β-carboline) moiety has been identified as a good pharmacophore for macrofilaricidal activity during search for new antifilarial agents. Macrofilaricidal activities of 1-substituted and 1,5-/1,6-/1,7- and 1,8-disubstituted-9*H*-pyrido[3,4-*b*]indoles, (**a)** and representatives of pyrido[3,4-*b*]imidazo[1,2-*c'*]quinazolo[4,5-*e*] and [4,5-*g*]indoles (**b** and **c**) have shown varying degree of antifilarial activity.[129-131] Amongst 1-aryl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate derivatives,[132] the most potent compounds were methyl 1-(4-methylphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**d**) and methyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**e**), which exhibited highest adulticidal and highest microflaricidal activity against *A. viteae* at 50 mg/kg x 5 days (ip) respectively. Another compound, 1-(4-chlorophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]indole (**f**) exhibited 94 %, 95 % and 62 % *in vivo* macrofilaricidal activity when administered intraperitoneally against *A. viteae*, *L.carinii* and *Brugia malayi* respectively.



9*H*-Pyrido[3,4-*b*]indoles

7.4. Phenylimidazo[1,2-*a*]pyridine

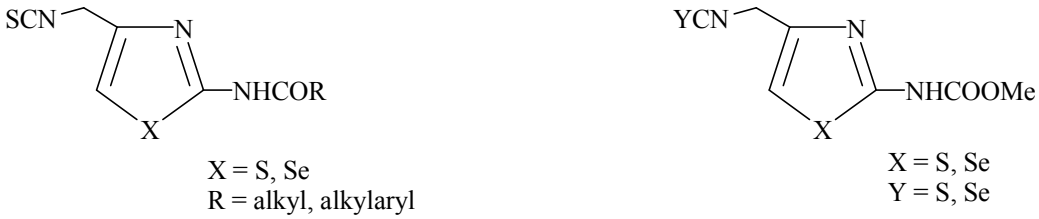
Recently, *bis*-amidine and *bis*-guanylhydrazone derivatives of substituted imidazo[1,2-*a*]pyridines have been synthesized and evaluated for their macrofilaricidal activity against *A. viteae* and *B.* pahangi.[133] One of the compound 6-guanylhydrazone-2-(4'-guanylhydrazonephenyl)-imidazo[1,2-*a*]pyridine has shown significant microfilaricidal activity against *A. viteae* at doses of 1.56-100 mg/kg.



Phenylimidazo[1,2-*a*]pyridine derivative

7.5. Disubstituted thiazole and selenazole derivatives

Kumar Y, et al[134] have synthesized and evaluated a series of 2-arylamido and 2-alkylamido derivatives of 2-amino-4-isothiocyanatomethyl)thiazole and 2-amino-4-(isothiocyanatomethyl) selenazole for their antifilarial activity but none of the compounds prepared in this study showed significant activity against the adult worms of *B. pahangi* and *A. vitae* in jirds. Consequently, a 2-methoxy carbamoyl group was designed into these compounds, to increase the efficacy for inhibition of microtubule assembly, which is the prominent mode of action of the anthelmintic benzimidazole carbamates. A series of methyl 4-(isothiocyanatomethyl)thiazole-2-carbamate and methyl 4-(isothiocyanatomethyl) selenazole-2-carbamate have been prepared.[135] One of the compounds (X = S, Y= S) demonstrated significant *in vivo* antifilarial activity against the adult worms of *Acanthocheilonema viteae* in experimentally infected jirds.



X = S, Se
R = alkyl, alkylaryl

X = S, Se
Y = S, Se

2,4-Disubstituted thiazoles and selenazoles

7.6. Quinolones

Few of the 6-carboxyquinol-4(1*H*)-one-3-carboxamides were found to possess significant antifilarial activity.[136, 137] These compounds, having macrofilaricidal and microfilaricidal activity combined with sterilization of the female worms, are attractive candidate for the treatment of filariasis. Some compounds also caused inhibition and death of adult male and female of *B. malayi*.

Quinolone derivatives

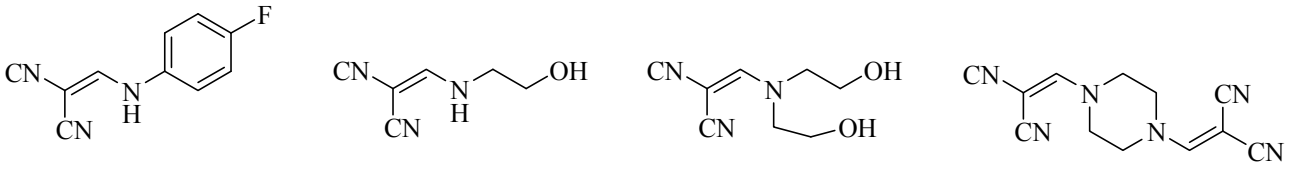
7.7. Aminoisoquinolines and aminoquinolines

Role of aminoquinolines and aminoisoquinolines as antimalarials is well documented but no sincere efforts have been carried out in exploring this pharmacophore as an antifilarial. Recently, aminoisoquolines and aminoquinolines with variety of substitutent at 5-, 8- and 4- positions have been reported to posses antifilarial activity.[138, 139] The micro and macro filarical activities of the synthesized compound were evaluated *in vivo* against *A. viteae* infection in *M. natalensis*. Few of the compounds have shown promising microfilaricidal, adulticidal activities combined with sterilization of female worms (> 80%) and offer useful lead to conduct further modification to generate potent antifilarial agents.

Aminoisoquinoline and aminoquinoline derivatives

7.8. Dicyano-2-(substituted) ethylenes

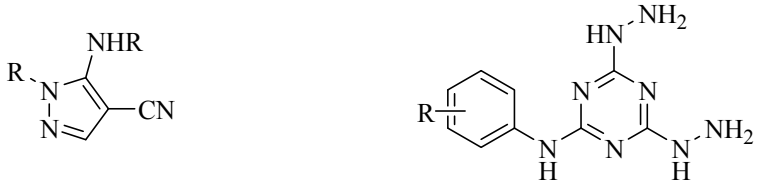
Few of the compounds having 1,1'dicyano-2-(substituted) ethylenes moiety have been reported to exhibit significant antifilarial activity. Some of the compounds shown below exhibited 91-76 % microfilaricidal activity when administered at dose of 50 mg/kg i.p.[140]



1,1'-Dicyano-2-(substituted)ethylenes

7.9. Pyrazoles and triazines

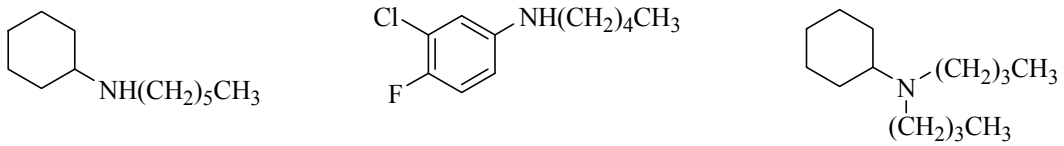
Several pyrazole and triazine derivatives were synthesized and evaluated as antifilarial agent. These compounds with microfilaricidal and adulticidal activity may be regarded as a potential candidate for antifilarial chemotherapy.[141, 142]



Pyrazole and triazine derivatives

7.10. Secondary amines

Secondary amines of the following structures have been recently investigated as pharmacophores for macrofilaricidal drug design. These compounds exhibited promising *in vivo* macrofilaricidal activity when administered orally. The most potent compound was found to be N-hexylcyclohexyl amine which showed 100 % adulticidal activity at 200 mg/kg.[143]



Secondary amine derivatives

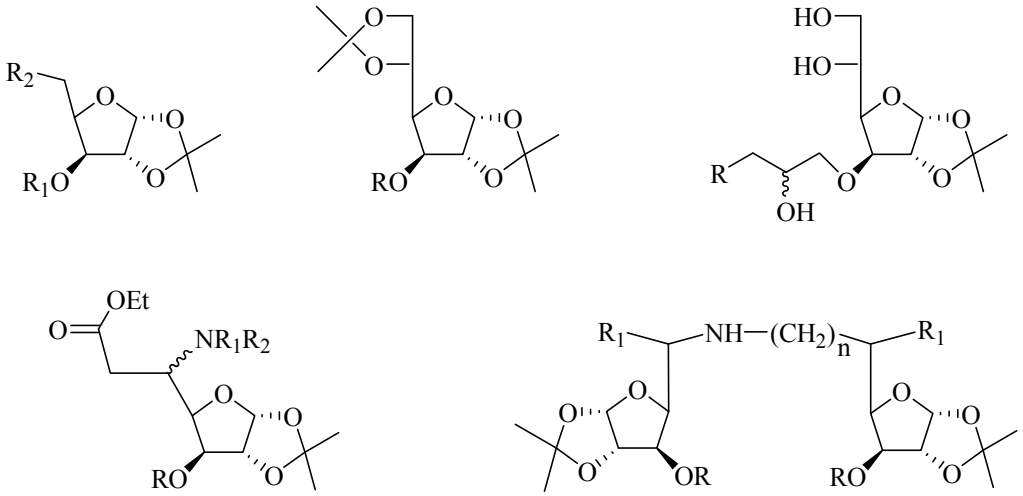
7.11. Epoxy sulphonamides and ethyne sulfonamides

Several 2-substituted 1,2-epoxyethanesulfonamides and ethynesulfonamides were synthesized and evaluated for their antifilarial activity against *Molinema dessetae* either *in vivo* or *in vitro* and most of the compounds were found to be active *in vitro*.[144, 145] Few of them also showed marked macrofilaricidal activity *in vivo* without any microfilaricidal activity. The differences between the *in vivo* and *in vitro* results may be due, in part, to the low chemical stability of the epoxy sulfonamides. Despite this limitation, the activities observed suggest the further development and testing of such compounds as macrofilaricides.

Sulphonamide derivatives

7.12. Carbohydrate derivatives

Several monosachharide derivatives have recently been reported from our group as potent antifilarial agents. The activity in these compounds is attributed to their action on enzymes involved in different metabolic pathways crucial for the survival of the filarial parasite. The compounds synthesized were evaluated for their filarial glutathione metabolizing, immunomodulatory and DNA topo-II inhibitory activities. Some of the compounds have shown potent *in vitro* and *in vivo* activities.[48, 146-150.]



Synthetic carbohydrate derivatives

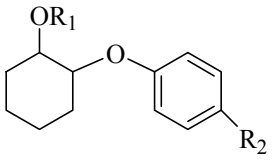
7.13. Vanillic acid analogs

Vanillic acid, isolated from the bark of *Melia azadarach*, has been reported for a broad spectrum anthelmintic activity. Recently, a number of vanillic acid analogues have been synthesized and evaluated against experimental filarial infections using cotton rats (*Sigmodon hispidus*) infected with *L. carinii*.[151] Few of the compounds exhibited potent micro and macro filaricidal activity (> 80 %) with sterilization of surviving female worms (80-100%).

Vanillic acid analogs

7.14. Phenoxy cyclohexane derivatives

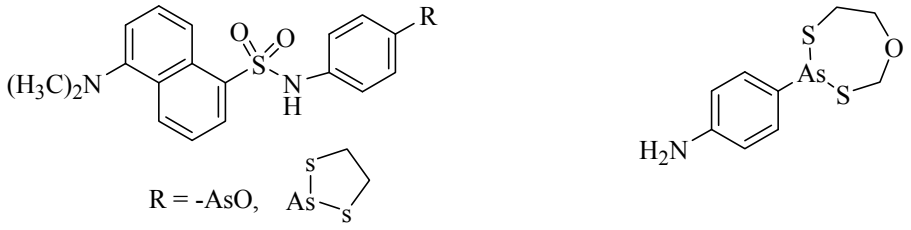
Several phenoxycyclohexane derivatives have been reported as potent inhibitor of phosphoenolpyruvate carboxylase (PEP-Carboxylase), which is involved in glycolysis and transforms phosphoenolpyruvate to oxaloacetate. Thus by targeting this enzyme, the metabolism of carbohydrate is inhibited, which appears to be a novel path for killing filarial parasites as carbohydrate is a major source of their energy. Phenoxycyclohexane derivatives inhibited the enzyme in a non-competitive manner and show promise *in vitro* activity in animal studies.[152]



Phenoxycyclohexane derivatives

7.15. Organometallic complexes

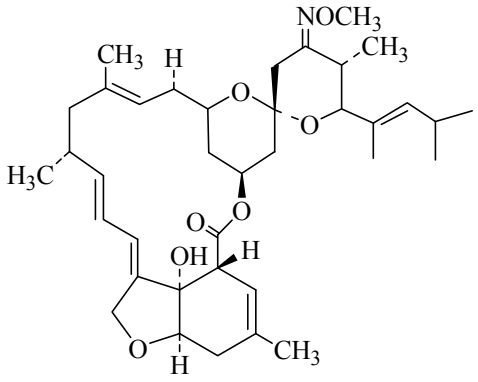
These compounds known for protozoicidal activities have also been evaluated for their *in vitro* antifilarial activity using two models: infective larvae of *Molinema dessetae* and adult female worms of *B. pahangi*. It was found that Ir(I)-COD-pentamidine tetraphenylborate has potent inhibitory activity in *M. dessetae*. Many other analogs have also shown potent antifilarial activity. Recently several trivalent organoarsenicals have also been shown to posses *in vitro* antifilarial activity against infective larvae of *M. dessetae*.[153]



Organometallic complexes

7.16. Moxidectin

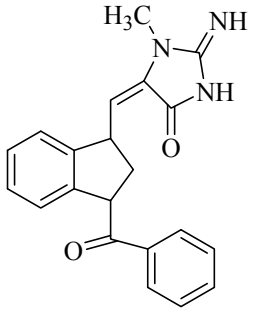
Moxidectin, a macrolide like avermectin, is currently in early clinical stages of evaluation for onchocerciasis. It is found to be more effective than ivermectin in most of the animal models and can be assessed as an alternative to ivermectin. The drug has potent effects on mf and results in long term sterilization of female adult worms, but there is no evidence as yet showing its macrofilaricidal action.[154]



Moxidectin

7.17. Aplysinopsin analog

A synthetic analog of the marine alkaloid aplysinopsin, 3-[(2'-imino-3'-methyl-5'-oxo-4'-imidazolidinylidene)methyl]-1-benzoyl-1H-indole has been reported to posses 90 %, and 64 % macrofilaricidal activity against *A. viteae* and *L. carinii* at doses of 50 mg/kg and 30 mg/kg respectively.[155]

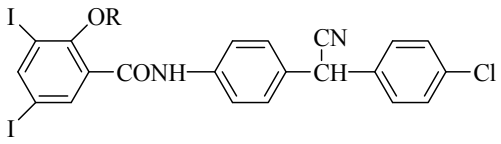


Aplysinopsin

7.18. Lymphotropic agents

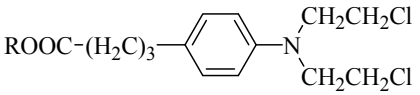
The use of lymphatic system rather than the blood is another fruitful approach for delivery of antifilarial drugs. Recently, anatomo-pathological studies have shown that all adult filarial worms were in contact with the lymphatic system and this approach may lead to the development of highly lymphotropic agents as potent macrofilaricide for use in filariasis chemotherapy. Several prodrugs of closental, chlorambucil and niclosamide, expected to accumulate in the lymphatic system, have been synthesized and evaluated for their activity on the filaria *M. dissetae* and few of them showed promise *in-vitro* activity. In case of closental and chlorambucil prodrugs the most active prodrug after treatment at 200 μmol/kg by the oral route was the 1,3-dipalmitoyl-2-succinyl-glycerol-closantel. The delayed macrofilaricidal effect of closantel prodrugs was of interest to prevent

anaphylactic shock. *In vitro*, chlorambucil was active on *M. dessetae* infective larvae with an IC_{50} of 26 μM. However, no activity with chlorambucil and its prodrngs was observed *in vivo*.[156]



R = H,	Closantel
R = Palmitoyl,	Palmitoyl closantel
R = 1,3-dipalmitoyl-2-succinyl glycerol,	1,3-dp-2-succinyl-glycerol closantel
R = 1,3-dipalmitoyl-2-succin-amide-2-amino glycerol,	1,3-dp-2-succinamido-2-amino glycerol closantel

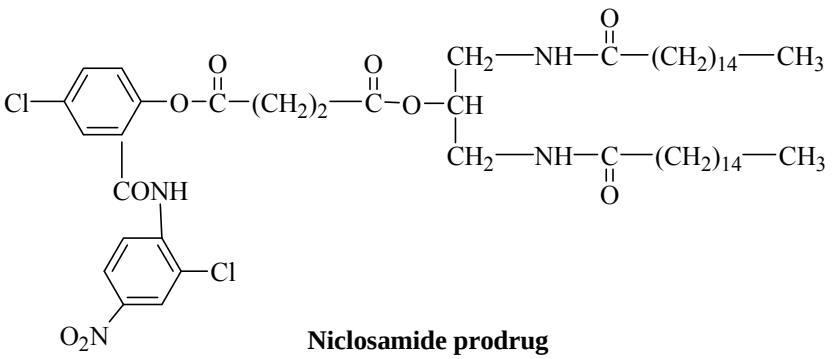
Chemical structure of closental and its prodrug



R = H,	Chlorambucil
R = 1,3-dipalmitoyl glycerol	1,3-dp-2-chlorambucil glycerol
R = 1,3-dihexadecyl thio glycerol,	1,3-dihexadecyl thio-2-chlorambucil glycerol

Chemical structure of chlorambucil and its prodrug

Niclosamide is regarded as a very effective agent against intestinal helmintic infections in man and animals. However, it does not exhibit significant antifilarial activity when orally administered at 200 μmol/kg. Its use as macrofilaricidal agent requires a modification of its resorption to reach the filarial parasite, which has lymphaticodermic or lymphatic localization. The 5 prodrugs were synthesized by bioisosteric replacement of the ester bond, linking the fatty acids to the glycerol backbone (1- and 3- position), with more hydrophilic (amide) or more lipophillic (thioether) function. The intrinsic antifilarial activity and the delayed effect of these compounds were evaluated *in vitro*. Then, *in vivo* tests were performed with *M. dessetae* infective larvae to select the best ligands. One of the prodrug (having a diamide function) was found responsible for an *in vitro* delayed effect and an orally *in vivo* activity (200 μmol/kg when administered in a single dose).[157]



Niclosamide prodrug

8. FUTURE PERSPECTIVES

Major advances in our understanding of several aspects of filariasis in the last few years will ultimately lead to improved means of controlling the filarial infections. A better knowledge of the epidemiological, pathological dynamics and immunological basis of infection of filarial disease can greatly contribute to control filariasis in a better manner. The introduction of new diagnostic tools like filarial antigen tests, ICT test, Ultrasonography and other have revolutionized treatment of filariasis. Annual mass treatment with Diethylcarbamizine (DEC) either alone or in combination with Ivermectin and Albendazole has been proven to be very effective in destroying microfilariae and interrupting transmission. With this knowledge and armed with these tools, the WHO goal of elimination lymphatic filariasis as a health threat by the year 2020 is achievable. But still there are lots of drawbacks that need to be re-evaluated by modern research methods. Our knowledge about precise filariasis cases is not validated and to know the exact estimate of filariasis other special analysis tools need to be employed so that the geographic distribution of filariasis can be accurately determined. Clinical diagnosis of acute filariasis is often difficult and can be confused with other febrile inflammatory illnesses. Thus, there is a need to develop and trial clinical checklist that will improve diagnosis, which can be done by improving the availability of standard kits for blood-sample collection, DNA isolation, PCR amplification, and DNA product detection and also by developing a multiplex PCR that could be used to detect and differentiate *Brugia* spp. and *Wuchereria* from other filarial parasites. There is an urgent need to develop simple, effective health promotion materials to inform people about the disease and its prevention. There must be research into innovative, cost-effective means of drug delivery. Although the drugs presently available appear to be very effective, there is still a great need to discover other anti-filarial drugs and emphasis should be given to the development of effective macrofilaricides with larvicidal properties. The identification and development of alternative antibiotics or regimens effective against *Wolbachia* that could be used in MDA (mass drug administration) programs and offer specific treatment to infected individuals should be entertained. Moxidectin should be evaluated for effectiveness against lymphatic filariasis (LF) parasites as soon as possible and should undergo clinical trials for evaluation of adulticidal or microfilaricidal activity in LF. More detailed understanding of the biochemical pathways unique to the parasite and not present in mammalian host provide a fruitful approach for the design of antifilarial drugs. With increased knowledge of parasite physiology a directed rational search for new lead should be possible. Development of techniques to monitor the emergence of drug resistance needs to be developed and trialed. As can

be seen in the foregoing, much progress has been made in filariasis research and control, but a large amount of work remains before afflict of filariasis is finally eliminated.

9. REFERENCES

1. (a)Ashford, R. W. and W, Crewe. Liverpool School of Trop Med, **1998,** Liverpool, United Kingdom. (b) Galvez Tan, J.Z. The elimination of Lymphatic filariasis: Astrategy for the poverty alleviation and sustainable development o: Perspective from Phillippines Filaria Journal **2003**; 2: 1-5 and references cited therein
2. Ambroise-Thomas, P. Parasitic diseases and immunodeficiencies. Parasitol, 2001; 122: S65.
3. (a) World health organization, Building partnerships for lymphatic filariasis-strategic plan. WHO, Geneva, 1999. (b) Ottesen, E.A.. The global programme to eliminate lymphatic filariasis. Tropical Medicine & International Health 2000; 5: 591-594.
4. Molyneux, D. Lymphatic Filariasis (Elephantiasis) Elimination: A public health success and development opportunity. Filaria Journal, 2003; 2: 2-13.
5. Ottesen, E. A. Filariasis now. Am J Trop Med Hyg, 1989; 4: S9
6. (a) Michael, E.; Bundy, D. A. P. Global mapping of lymphatic filariasis. Parasitol Today, 1997; 13; 472.(b) World Health Organisation: Geneva, Switzerland, Fact Sheet No. 102, 2000; http://www.who.int/mediacentre/factsheets/fs102/en (c) World Health Organisation, WHO report 2002; www.who.int/tdr/disease/lymphfil/htm. (d) Khan, A.M.; Mahanta J., Lymphatic Filariasis Eradication Programme. Curr. Sci. 2005; 88:1359-1360.
7. Das, P.K.; Pani, S.P. Towards elimination of lymphatic filariasis in India: Problems, Challenges, opportunities and new limitations J. Int. Med. Sci. Acad. 2000; 13: 18-26 and references citedtherein.
8. (a) Hoerauf, A.; Volkmann, L.; Hamelmann, C.; Adjei, O.; Autenrieth, I. B.; Fleischer, B.; Buttner, D. W. Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis**.** Lancet, 2000; 355: 1242. (b) Behbehani, K. Candidate parasitic diseases. Bull. WHO (Suppl.2), 1998; 76: 64. (c) Ottesen, E. A.; Duke, B. O. L.; Karam, M.; Behbehani, K. Strategies and tools for the control/elimination of lymphatic filariasis. Bull, W. H. O, 1997; 75: 491. (d) Collier, L.; Balows, A.; Sussman, M. Parasitol, 1998, Vol 5, Topley and Wilkin's, 9th edn, Arnold, London.

9. Dzodzomenyo, M.; Dunyo, S. K.; Ahorlu, C. K.; Coker, W. Z.; Appawu, M. A.; Pedersen, E. M.; Simonsen, P. E. Bancroftian filariasis in an irrigation project community in Southern Ghana.Trop Med Int Health, 1999,; 4: 13.
10. Dhanda, V.; Das, P. K.; Lal , R.; Srinivasan, R.; Ramaiah, K. D.; Spread of lymphatic filariasis, re-emergence of leishmaniasis and threat of babesiosis in India. Indian J Med Res. 1996;103:46–54.
11. McMahon, J. E.; Simonsen, P. E. 20th edition, edited by Cook, G. C. W.B. Saunders Company London, 1996, Chap. 70.
12. Roberts, L. S.; Janovy, J. In: Schmidt GD, Robers LS. Foundations of Parasitology 5th. Edition, chapter 29. WCB publishers Boston 1996.
13. (a) Pinder, M. Loa loa — a neglected filaria. Parasitol Today, 1988; 14: 279. (b) Boussinesq. M and Gardon. J. Prevalances of Loa loa microfilaraemia throughout the area endemic for the infection. Ann Trop Med Parasitol, 1997; 91: 573.

.

14. (a) Ottesen, E. A. The human filariasis: New understandings, new therapeutic strategies. Curr Opin Inf Dis, 1994; 7: 550-558. (b) Freedman, D. O.; de Almeida Filo, M. J.; Besh, S.; de Silva, M. C.; Braga, C.; Maciel, A.; Furtado, A. F. Abnormal lymphatic function in presymptomatic bancroftian filariasis J. Inf. Dis, 1995; 171: 997.
15. (a) Dunyo, S. K.; Nkrumah, F. K.; Ahorlu, C.K.; Simonsen, P.E. Exfoliative skin manifestations in acute lymphatic filariasis. Trans R Soc Trop Med Hyg, 1998; 92: 539-40 (b) Dreyer, G.; Medeiros, Z.; Netto, M. J.; Leal, N. C.; de Castro, L. G.; Piessens, W. F. Acute attacks in the extremities of persons living in an area endemic for bancroftian filariasis differentiation of two syndromes. Trans R Soc Trop Hyg, 1999; 93: 413.
16. (a) Burri, H.; Loutan, L.; Kumaraswami, V.; Vijayasekaran, V. Skin changes in chronic lymphatic filariasis. Trans R Soc Trop Med Hyg, 1996; 90: 671. (b) Gyapong, J. O.; Webber, R. H.; Morris, J.; Bennett, S. Prevalance of hydrocele as a rapid diagnostic index for lymphatic filariasis. Trans R Soc Trop Med Hyg, 1998; 92: 40.
17. (a) Partono, F. Diagnosis and treatment of lymphatic filariasis. Parasitol Today, 1985; 1: 52. (b) Dreyer, G.; Noroes, J.; Addiss, D. The silent burden of sexual disability associated with lymphatic filariasis. Acta Trop, 1997; 63: 57. (c) Evans, D. B.; Gelband, H.; Vlassoff, C. Social and economic factors and the control of lymphatic filariasis: a review. Acta Trop, 1993; 53: 1.

18. (a) Kolekar, S.; Sundaram, P.; Joshi, J. M. Unusual diagnostic aid for a common tropical disease. Indian J Chest Dis Allied Sci. 2003; 45(4): 257-9. (b) Dreyer, G.; Dreyer, P.; Piessens, W. F. Extralymphatic disease due to bancroftian filariasis. Braz J Med Biol Res. 1999; 32(12):1467-72. (c) Langhammer, J.; Birk, H. W.; Zahner, H. Renal disease in lymphatic filariasis : evidence for tubular and glomerular disorders at various stages of the infection..Trop. Med. Int .Health, 1997; 2: 875.

19. Wahl. G.; Georges. A, J. Current knowledge on the epidemiology, diagnosis,immunology,and treatment of loiasis. Trop Med Parasitol, 1995; 46: 287.

20. (a) Devaney, E.; Martin, S. A. M.; Thompson, F. J. Stage specific gene expression in lymphatic filarial mematodes. Parasitol Today, 1996; 12: 418.

21. Simonsen, P. E.; Niemann, L.; Meyrowitsch, D. W. Wuchereria bancrofti in Tanzania: microfilarial periodicity and effect of blood sampling time on microfilarial intensities. Trop Med Int Health, 1997; 2: 153

.

22. (a) Youssef, F. G.; Hassanein, S. H.; Cummings, C. E. A modified staining method to detect Wuchereria bancrofti microfilariae in thick-smear preprations. Ann Trop Med Parasitol, 1995; 89; 93. (b) Melrose, W. D.; Turner, P. F.; Pisters, P.; Turner, B. An improved Knott's concentration test for the detection of microfilariae. Trans R Soc Trop Med Hyg, 2000; 94: 176.

23. Moulia-Pelat, J.P.; Glaziou, P.; Nguyen-Ngoc, L.; Cardines, D.; Spiegel, A.; Cartel, J.L. A comparative study of detection methods for evaluation of microfilaremia in lymphatic filariasis control programmes. Trop Med Parasitol. 1992; 43(3):146-8.

24. (a) Fischer, P.; Wibowo, H.; Pischke, S.; Ruckert, P.; Liebay, E.; Ismid, I. S.; Supali, T. PCR-based detection and identification of the filarial parasite Brugia timori from Alor island,Indonesia. Ann Trop Med Parasitol, 2002; 96: 809. (b) Toure, F. S.; Mavoungo, E.; Kassambara, L.; Williams, T.; Wohl, G.; Millet, P.; Egwang, T. G. Human occult loiasis: field evaluation of a nested polymerase chain reaction assay for the detection of occult infection. Trop Med Int Health, 1998; 3: 505. (c) Goodman, D. S.; Orelus, J. N.; Roberts, J. M.; Lammie, P. J.; Streit, T. G. PCR and Mosquito dissection as tools to monitor filarial infection levels following mass treatment. Filaria Journal, 2003; 2: 11.

25. Fischer, P.; Liu, X.; Lizotte-Waniewski, M.; Kamal Ibrahim, H.; Ramzy Reda, M. R.; Williams, S. A. Development of a quantitative, competitive polymerase chain reaction--

enzyme-linked immunosorbent assay for the detection of Wuchereria bancrofti DNA. Parasitol Res, 1999; 85: 176.

26. (a) More, S. J.; Copeman, D. B. A highly specific and sensitive monoclonal antibody-based ELISA for the detection of circulating antigen in bancroftian filariasis. Trop Med Parasitol, 1990; 41: 403. (b) Rahmah, N, et al. A recombinant antigen based IgG4 ELISA for the specific and sensitive detection of Brugia Malayi infection. . Trans R Soc Trop Med Hyg, 2001; 95: 280.
27. Weil,G.J.;Lammie,P.J.;Weiss,N. The ICT Filariasis Test: A rapid-format antigen test for diagnosis of bancroftian filariasis. Parasitol today, 1996; 12: 401.
28. (a) Amaral, F.; Dreyer, G.; Figueredo-Silva, J.; Noroes, J.; Cavalcanti, A.; Sanico, S. C.; Santos, A.; Coutinho, A. Live adult worms detected by ultrasonography in human Bancroftian filariasis. Am J Trop Med Hyg, 1994; 50: 735. (b) Freedman, D. O.; de Almeida Filo, M. J.; Besh, S.; de Silva, M. C.; Braga, C.; Maciel, A. Lymphoscintigraphic analysis of lymphatic abnormalities in symptomatic and asymptomatic human filariasis. J Infect Dis. 1994;170: 927.
29. Gupta, S.; Srivastava, A.K. Biochemical targets in filarial worms for selective antifilarial drug design. Acta. Parasitologica , 2005; 50: 1-18.
30. (a) Lammie, P. J.; Weil, G. J.; Rahmah, N.; Kaliraj, P.; Steel, C.; Goodman D, Lakshmikanthan, V. B.; Ottesen, E. Recombinant antigen-based antibody assays for the diagnosis and surveillance of lymphatic filariasis - a multicenter trial. *Filaria J*, 2004; 3: 9. (b) Klion, A. D.; Vijaykumar, A.; Oei, T.; Marlin, B.; Nutman, T. B. Serum immunoglobulin G4 antibodies to the recombinant antigen, Ll-SXP-1, are highly specific for Loa loa infection. J Infect Dis, 2003; 187: 128-33.
31. Robertson, S. J.; Martin, R. J. Levamisole-activated single-channel currents from muscle of the nematode parasite Ascaris suum. British J Pharmacol, 1993; 108: 170.
32. Evans, A. M.; Martin, R. J. Activation and cooperative multi-ion block of single nicotinic-acetylcholine channel currents of Ascaris muscle by the tetrahydropyrimidine anthelmintic, morantel. British J Pharmacol, 1996; 118:1127.
33. Martin, R. J. Gamma-Aminobutyric acid- and piperazine-activated single-channel currents from Ascaris suum body muscle. British J Pharmacol, 1985; 84: 445.
34. Arena, J. P. Expression of Caenorhabditis elegans mRNA in n Xenopus oocytes: a model system to study the mechanism of action of avermectins. *Parasitol Today*, 1994; 10, 35.

35. (a) Cull, D. F.; Vassilatis, D. K.; Liu, K. K.; Paress, P. S.; Vanderploeg, L. H.; Schaeffer, J. M. Cloning of an avermectin-sensitive glutamate-gated chloride channel from Caenorhabditis elegans. Nature, 1994; 371: 707. (b) Cull, D. F.; Wilkinson, H.; Vassilatis, D. K.; Etter, A.; Arena, J. P. Molecular biology and electrophysiology of glutamate-gated chloride channels Parasitol, 1996; 113: 191.
36. (a)Tang, L.; Prichard, R.K. Characterisation of tubulin from Brigia malayi and Brugia pahangi. Mol. Bioche. Parasitol. 1989; 32: 145-152.(b) Howells, R. E.; Delves, C. J. A. Simple method for the identification of compounds which inhibit tubulin polymerization in filarial worms. Ann Trop Med Parasitol. 1985 ;79(5):507-12.

37. Lacey, E.; Gill, J. H. Biochemistry of benzimidazole resistance. *Acta Trop*, **1994**, *56*, 245.
38. Liu, L. X.; Weller, P. F. Arachidonic acid metabolism in filarial parasites.Exp. Parasitol, 1990; 71 (4): 496-501.
39. Martin, R. J.; Robertson, A. P.; Bjorn, H. Target sites of anthelmintics. Parasitol, 1997; 114: 111.
40. Longworth, D. L.; Monahan-Earley, R. A.; Dvorak, A. M.; Weller, P. F.. Brugia malayi: arachidonic acid uptake into lipid bodies of adult parasites. Exp Parasitol. 1988 ;65(2):251-7.
41. (a) Sies, H. Strategies of antioxidant defense Eur J Biochem, 1993; 215; 213. (b) Yu, B. P. Cellular defenses against damage from reactive oxygen species. Physiol Rev,1994; 74: 139.
42. Murray, E. S.; Vincent P. S.; Thomas, G. R.; Gounaris, K. Resistance of filarial nematode parasites to oxidative stress. Int J Parasitol, 1998; *28(9)*: 1315 -1332 and references cited therein.
43. (a) Darley-Usmar, V. M.; Hogg, N.; O'Leary, V. J.; Wilson, M. T.; Moncada, S. The simultaneous generation of superoxide and nitric oxide can initiate lipid peroxidation in human low density lipoprotein. Free Radical Res Commun**,** 1992**;**17**:** 9**.** (b) Henkle-Dührsen, K.; Tuan, R. S.; Wildenburg, G. Localization and functional analysis of the cytosolic and extracellular CuZn superoxide dismutases in the human parasitic nematode Onchocerca volvulus. Mol Biochem Parasitol, 1997;88**:** 187.
44. (a) Lu, W.; Egerton, G. L.; Bianco, A. E.; Williams, S. A. Thioredoxin peroxidase from Onchocerca volvulus: a major hydrogen peroxide detoxifying enzyme in filarial parasites**.**

Mol Biochem Parasitol, 1998; 91; 221. (b) Ghosh, I.; Eisinger, S. W.; Raghavan, N.; Scott, A. L. Thioredoxin peroxidases from Brugia malayi**.** Mol Biochem Parasitol, 1998; 91; 207-220.

45. (a) Esworthy, R. S.; Chu, F-F.; Geiger, P.; Girotti, A. W.; Doroshow, J. H. Reactivity of plasma glutathione peroxidase with hydroperoxidesubstrate and glutathione. Arch Biochem Biophys, 1993; 307: 29. (b) Muller, S.; Gilberger, T. W.; Fairlamb, A. H.; Walter, R. D. Molecular characterization and expression of Onchocerca volvulus glutathione reductase Biochem J, 1997; 325: 645.
46. (a) Halliwell, B.; Gutteridge, J. M. The antioxidants of human extracellular fluids Arch Biochem Biophys, 1990; 280: 1. (b) Smith, V. P.; Selkirk, M. E.; Gounaris, K. Brugia malayi: resistance of cuticular lipids to oxidant-induced damage and detection of alpha-tocopherol in the neutral lipid fraction. Exp Parasitol, 1998; 88:103.
47. (a) Pandya, U.; Saxena, J. K.; Shukla, O. P. Filarial DNA and its interaction with polyamines and antifilarial drugs J Helminthol, 1997; 71; 325. (b) Kinnamon, K. E.; Engle, R. R.; Poon, B. T.; Ellis, W. Y.; McCall, J. W.; Dzimianski, M. T. Polyamines: agents with macrofilaricidal activity Ann Trop Med Parasitol, 1999; 93(8): 851.
48. Pandya, U.; Saxena, J. K.; Kaul, S. M.; Murthy, P. K.; Chatterjee, R. K.; Tripathi, R. P.; Bhaduri, A. P.; Shukla, O. P. DNA topoisomerases of filarial parasites: effect of antifilarial compounds. Med Sci Res., 1999; 27:103–106
49. Maxwell, A The interaction between coumarin drugs and DNA gyrase. Mol Microbiol, 1993; 9(4): 681.
50. (a) Williams, S. A.; Johnston, D. A. Parasitol, 1999; 118; S19. (b) Degrave, W. M.; Melville, S.; Ivens, A.; Aslett, M. Parasite genome initiatives Int J Parasitol, 2001; 31: 531. (c) Unnasch, T. R. The filarial genome project. Parasitol Today, 1994; 10: 415.
51. (a) Diatchenko, L.; Lau, Y. F.; Campbell, A. P.; Chenchik, A.; Moqadam, F.; Huang, B.; Lukyanov, S.; Lukyanov, K.; Gurskaya, N.; Sverdlov, E. D.; Siebert, P. D. Suppression subtractive hybridization: a method for generating differentially regulated or tissue-specific cDNA probes and libraries. Proc Natl Acad Sci U S A, 1996; 93: 6025. (b) Parkinson, J.; Mitreva, M.; Hall, N.; Blaxter, M.; McCarter, J. P. Trends Parasitol, 2003; 19: 283.
52. Williams, S. A.; Lizotte-Waniewski, M. R.; Foster, J.; Guiliano, D.; Keddie, E. M.; Higazi, T.; Unnasch, T. R. The mitochondrial genome of Onchocerca volvulus: sequence, structure and phylogenetic analysis. Mol Biochem Parasitol, 1998; 95: 111.

53. Shu, L.; Katholi, C. R.; Higazi, T.; Unnasch, T. R. Analysis of the Brugia malayi HSP70 promoter using a homologous transient transfection system. Mol Biochem Parasitol, 2003; 128: 67.

54. Aboobaker, A. A.; Blaxter, M. L. Use of RNA interference to investigate gene function in the human filarial nematode parasite Brugia malayi. Mol Biochem Parasitol, 2003; 129: 41.

55. Taylor, M. J.; Hoerauf, A. Wolbachia bacteria of filarial nematodes. Parasitol Today, 1999; 15: 437.

56. (a) Taylor, M. J. Wolbachia bacteria of filarial nematodes: a target for control? Parasitol. Today, 2000; 16: 179. (b) Taylor, M. J.; Cross, H. F.; Bilo, K. Inflammatory responses induced by the filarial nematode Brugia malayi are mediated by lipopolysaccharide-like activity from endosymbiotic Wolbachia bacteria J Exp Med, 2000; 191: 1429.

57. (a) Townson, S.; Hutton, D.; Siemienska, J.; Hollick, L.; Scanlon, T.; Tagboto, S. K.; Taylor, M. J. Antibiotics and Wolbachia in filarial nematodes: antifilarial activity of rifampicin, oxytetracycline and chloramphenicol against Onchocerca gutturosa, Onchocerca lienalis and Brugia pahangi.. Ann Trop Med Parasitol, 2000; 94: 801. (b) Smith, H. L.; Rajan, T. V. Tetracycline inhibits development of the infective-stage larvae of filarial nematodes in vitro. Exp. Parasitol, 2000; 95: 265.

58. Ottesen, E. A.; Duke, B. O.; Karam, M.; Behbehani, K. Strategies and tools for the control/elimination of lymphatic filariasis. Bull World Health Organisation, 1997; 75: 491.

59. (a) Maxwell, C. A.; Mohammed, K.; Kismuku, U.; Curtis, C. F. Can vector control play a useful supplementary role against bancroftian filariasis? *Bull World Health Organisation*, **1999**, *77*, 138. (b) Morel, C. M. Reaching maturity - 25 years of the TDR. Parasitol Today, 2000; 16(12): 522-528.

60. Charlwood, J. D.; Dagoro, H. Impregnated bed nets for the control of filariasis transmitted by Anopheles punctulatus in rural Papua New Guinea. Papua New Guinea Med J, 1987; 30: 199.

61. (a) Maizels, R. M.; Denham, D. A. Diethylcarbamazine (DEC): immunopharmacological interactions of an anti-filarial drug. Parasitol, 1992; 105: S49. (b) Ali, M. M.; Mukhtar, M. M.; Baraka, O. Z.; Homeida, M. M.; Kheir, M. M.; Mackenzie, C. D. Immunocompetance may be important in the effectiveness of mectizan (ivermectin) in the treatment of human onchocerciasis. Acta Trop, 2002; 84: 49.

62. (a) Chenthamarakshan, V.; Reddy, M. V. R.; Harinath, B. C. Immunoprophylactic potential of a 120 kDa Brugia malayi adult antigen fraction, BmA-2, in lymphatic filariasis. Parasite Immunol, 1995; 17: 277. (b) Dissanayake, S.; Perler, F. B.; Xu, M.; Southworth, M. W.; Yee, C. K.; Wang, S.; Dreyer, G.; Watawana, L.; Kurniawan, A.; Furhrman, J. A.; Piessens, W. F. Differential recognition of microfilarial chitinase, a transmission-blocking vaccine candidate antigen, by sera from patients with Brugian and Bancroftian filariasis Am J Trop Med Hyg, 1995; 53: 289. (c) Grieve, R. B.; Wisnewski, N.; Frank, G. R.; Tripp, C. A. Vaccine research and development for the prevention of filarial nematode infections. Pharmaceut Biotech, 1995; 6: 737.

63. Wang, S. H.; Zheng, H. J.; Dissanayake, S.; Cheng, W. F.; Tao, Z. H.; Lin, S. Z.; Piessens, W. F. Evaluation of recombinant chitinase and SXP1 antigens as antimicrofilarial vaccines. Am J Trop Med Hyg, 1997; 56: 474.

64. Zang, X.; Yazdanbakhsh, M.; Jiang, H.; Kanost, M. R.; Maizels, R. M. A novel serpin expressed by blood-borne microfilariae of the parasitic nematode Brugia malayi inhibits human neutrophil serine proteinases. Blood, 1999; 94: 1418.

65. (a) Le Goff, L.; Lamb, T. J.; Graham, A. L.; Harcus, Y.; Allen, J. E. IL-4 is required to prevent filarial nematode development in resistant but not susceptible strains of mice. Int J Parasitol, 2002; 32:1277. (b) Bleiss, W.; Oberlander, U.; Hartmann, S.; Adam, R.; Marko, A.; Schonemeyer, A.; Lucius, R.. Protective immunity induced by irradiated third-stage larvae of the filaria Acanthocheilonema viteae is directed against challenge third-stage larvae before molting.. J Parasitol, 2002; 88: 264. (c) Martin, C.; Al-Qaoud, K. M.; Ungeheuer, M. N.; Paehle, K.; Vuong, P. N.; Bain, O.; Fleischer, B.; Hoerauf, A. IL-5 is essential for vaccine-induced protection and for resolution of primary infection in murine filariasis. Med Microbiol Immunol (Berl), 2000; 189: 67. (d) Lustigman, S.; James, E. R.; Wilson, T.; Abraham, D. IL-4 is required to prevent filarial nematode development in resistant but not susceptible strains of mice. Trends Parasitol, 2002; 18:135.

66. Lowrie, R. C.; Eberhard, M, L.; Lammie, P. J.; Raccurt, C. P.; Katz, S. P.; Duverseau, Y. Uptake and development of Wuchereria bancrofti in Culex quinquefasciatus that fed on Haitian carriers with different microfilaria densities. T. Am J Trop Med Hyg, 1989; 41: 429.

67. Woolhouse, M. E. J.; Dye, C.; Etard, J. F.; Smith, T.; Charlwood, J. D.; Garnett, G. P.; Hagan, P.; Hii, J. L. K.; Ndhlovu, P. D.; Quinnel, R. J.; Watts, C. H.; Chandiwana, S. K.;

Anderson, R. M. Heterogeneities in the transmission of infectious agents: implications for the design of control programs. Proc United States Acad Sc, 1997;94: 338.

68. Molyneux, D. H.; Bradly, M.; Hoerouf, A.; Kyelen, D.; Taylor, J. M. Mass drug treatment for lymphatic filariasis and onchocerciasis. Trends Parasitol, 2003; 19(11): 516.
69. (a) James, D. M.; Gillies, H. M. John Wiley and Sons, Brisbane 1985. (b) Campbell WC, Rew RS. Plenum Press, New York, 1986.
70. Howells, R. E.; Medis, A. M.; Bray, P. G. The mode of action of suramin on the filarial worm Brugia pahangi. Parasitol, 1983; 87: 29.
71. Sharma, S. Vector-borne diseases. Prog Drug Res, 1990; 35: 365.
72. (a) Duke B. O. L. Letter : The effect of levamisole on Onchocerca volvulus. Trans R Soc Trop Med Hyg, 1974; 68: 1. (b) McMahon J. E. Preliminary screening of antifilarial activity of levamisole and amodiaquine on Wuchereria bancrofti. Ann Trop Med Parasitol, 1979; 73: 465.
73. (a) Molyneux, D.H. and Taylor, M. J. Current status and future prospects of the Global Lymphatic Filariasis Programme. Curr Opin Infect Dis, 2001; 14: 155. (b) Molyneux, D. H.; Zagaria, N. Lymphatic filariasis elimination: progress in global programme development. Ann Trop Med Parasitol, 2002; 96 (Suppl 2), S15.
74. Richards, F.O. Jr.; Boatin, B.; Sauerbery, M.; Seketeli, A. Control of onchocerciasis today: status and challenges Trends Parasitol, 2001; 17: 558.
75. Santiago-Stevenson, D.; Oliver-Gonzalez, J.; Hewitt, R. I. Treatment of filariasis bancrofti with 1-diethylcarbamyl-4-methyl-piperazine hydrochloride J Am Med Assoc, 1947; 135: 708.
76. MacKenzie, C. D.; Kron, M. A. Diethyl carbamazine: a review of its action in onchocerciasis, lymphatic filariasis and inflammation. Trop Dis Bull, 1985; 82 : R1.
77. Maizels, R. M.; Denham, D. A. Diethylcarbamazine (DEC): immunopharmacological interactions of an anti-filarial drug. Parasitol, 1992; 105: S49.
78. Mitsui, Y.; Aoki, Y. A direct competitive ELISA for the simple, sensitive and accurate determination of diethylcarbamazine concentration in serum. Int J Parasitol, 1998; 28; 623.
79. (a) Jing-yuan L. et al. Southeast Asian J Trop Med Pub Health, 1991; 22: 147. (b) Jing-yuan, L.; Zi C, Xiao-hong. H.; Zhao-ping, T. Mass treatment of filariasis using DEC-medicated salt. J Tropical Med Hyg, 1992; 95:132.

80. (a) Ismail, M.M.; Weil, G. J.; Jayasinghe, K. S.; Premaratne, U. N.; Abeyewickreme, W.; Rajaratnam, H. N.; Sheriff, M. H.; Perera, C. S.; Dissanaike, A. S. Prolonged clearance of microfilaraemia in patients with bancroftian filariasis after multiple high doses of ivermectin or diethylcarbamazine. Trans R Soc Trop Med Hyg, 1996; 90: 684. (b) Weil, G. J.; Sethumadhavan, K. V. P.; Santhanam, S.; Jain, D. C.; Ghosh, T. K. Persistence of parasite antigenemia following diethylcarbamazine therapy of bancroftian filariasis. Am J T Med Hyg, 1988; 38: 589-95.
81. (a) Eberhard, M. L.; Hightower, A. W.; Addiss, D. G.; Lammie, M. J. Clearance of Wuchereria bancrofti antigen after treatment with diethylcarbamazine or ivermectin. Am J Trop Med Hyg, 1997; 57; 483-6. (b) Noroes, J.; Dreyer, G.; Santos, A.; Mendes, V. G.; Medeiros, Z.; Addiss, D. Assessment of the efficacy of diethylcarbamazine on adult Wuchereria bancrofti in vivo. Trans R Soc Trop Med Hyg, 1997; 91: 78.
82. World Heath Organisation expert committee on filariasis. Lymphatic filariasis: diagnosis and pathogenesis. WHO expert committee on filariasis. Bull World Health Org, 1993; 71: 135.
83. Michael, E.; Meyrowitsch, D. W.; Simonsen, P. E Cost and cost effectiveness of mass diethylcarbamazine chemotherapy for the control of bancroftian filariasis: comparison of four strategies in Tanzania.. Trop Med Int Health, 1996; 1: 414.
84. (a) Gelband, H. Diethylcarbamazine salt in the control of lymphatic filariasis. Am J Trop Med Hyg, 1994; 50: 655-62. (b) Shenoy, R. K.; Varghese, J.; Kuttikkal, V. V. The efficacy , tolerability and safe of diethylcarbamazine – fortified salt in the treatment of the microfilaraemias of brugian filariasis : an open , hospital based study. Ann Trop Med Parasitol, 1998;92(3): 285-93.
85. Kimura, E.; Mataika, J. U. Control of lymphatic filariasis by annual single-dose diethylcarbamazine treatments. Parasitol Today, 1996; 12: 240.
86. Taylor, M. J.; Turner, P. F. Control of lymphatic filariasis Parasitol Today, 1997; 13: 85.
87. (a) Bird, A. C.; Sheikh, H. E.; Anderson. J.; Fuglsang, H. Changes in visual function and in the posterior segment of the eye during treatment of onchocerciasis with diethylcarbamazine citrate Br J Ophthalmol, 1980; 64: 191-200. (b) Aziz, M. A. Chemotherapeutic approach to control of onchocerciasis. Rev Infect Dis, 1986; 8; 500. (c) Carme, B.; Boulesteix, J.; Boutes, H.; Puruehnce, M. F. Five cases of encephalitis during treatment of loiasis with diethylcarbamazine. Am J Trop Med Hyg, 1991; 44(6): 684-90.

88. Dreyer, G.; Pires, M. L.; Andrade, L. D.; Lopes, E.; Medeiros, Z.; Tenorio, J.; Coutinho, A.; Norões, J.; Figueredo-Silva, J. Tolerance of diethylcarbamazine by microfilaraemic and amicrofilaraemic individuals in an endemic area of Bancroftian filariasis, Recife, Brazil. Trans R Soc Trop Med Hyg, 1994; 88; 232.

89. Maizels, R. M.; Denham, D. A. Diethylcarbamazine (DEC): immunopharmacological interactions of an anti-filarial drug. *Parasitol*, **1992**, *105*, S49.

90. (a) Schares, G.; Hofmann, B.; Zahner, H. Antifilarial activity of macrocyclic lactones: comparative studies with ivermectin, doramectin, milbemycin A4 oxime, and moxidectin in Litomosoides carinii, Acanthocheilonema viteae, Brugia malayi, and B. pahangi infection of Mastomys coucha. Trop Med Parasitol. 1994 ; 45(2):97-106. (b) Campbell, W. C. Ivermectin as an antiparasitic agent for use in humans. Ann Rev Microbiol, 1991; 45: 445.

91. (a) Ottesen, E. A.; Campbell, W. C. Ivermectin in human medicine. J. Antimicrob Chemother, 1994; 34; 195. (b) Townson, S.; Tagboto, S. K.; Castro, J.; Lujan, A.; Awadzi, K.; Titanji, V. P. K. Comparison of the sensitivity of different geographical races of Onchocerca volvulus microfilariae to ivermectin: studies in vitro. Trans R Soc Trop Med Hyg, 1994; 88: 101.

92. Goa, K. L.; McTavish, D.; Clissold, S. P. Ivermectin. A review of its antifilarial activity, pharmacokinetic properties and clinical efficacy in onchocerciasis. Drugs, 1991; 42; 640.

93. Dreyer, G.; Addiss, D.; Noroes, J.; Amaral, F.; Rocha, A.; Coutinho, A.ultrasonographic assessment of the adulticidal efficacy of repeat high-dose ivemectin in bacroftian filariasis. Trop Med Int Health, 1996; 1: 427.

94. (a) Twum-Danso, N. A. Y. Loa loa encephalopathy temporally related to ivermectin administration reported from onchocerciasis mass treatment programs from 1989 to 2001: implications for the future. Filaria J, 2003; 2 (Suppl 1): S7. (b) Mackenzie, C. D.; Geary, T. G.; Gerlach, J. A. Possible pathogenic pathways in the adverse clinical events seen following ivermectin administration to onchocerciasis patients. Filaria J, 2003; 2 (Suppl 1): S5.

95. (a). Boussinesq, M.; Gardon, J.; Gardon-Wendel, N.; Chippaux, J. P. Clinical picture, epidemiology and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. Filaria J, 2003; 2 (Suppl 1): S4. (b) Duke, B. O. L. Overview: Report of a Scientific Working Group on Serious Adverse

Events following Mectizan(R) treatment of onchocerciasis in Loa loa endemic areas. Filaria J, 2003; 2 (Suppl 1): S1.

96. (a) Subrahmanyam, D. Antifilarials and their mode of action. Ciba Found Symp, 1987; 127: 246. (b) Harder, A. Chemotherapeutic approaches to nematodes: current knowledge and outlook. Parasitol Res, year ? 88, 272 and references cited therein.
97. Hawking, F. Suramin: with special reference to onchocerciasis. Adv Pharmacol Chemother, 1978;15:289.
98. (a) Awadzi, K. Clinical picture and outcome of Serious Adverse Events in the treatment of Onchocerciasis. Filaria J, 2003; 2 (Suppl 1): S6. (b) Gonzalez, Guerra. L.; Rasi, E.; Rivas, a. [partial account (752 cases) of the treatment of onchocerciasis in venezuela with suramin sodium.] rev Venez Sani Asist Soc Caracas, 1964;29:90.
99. Thylefors, B.; Rolland, A. The risk of optic atrophy following suramin treatment of ocular onchocerciasis. Bull World Health Organisation, 1979; 57: 479.
100. Rivas-Alcala, A. R.; Greene, B. M.; Taylor, H. R.; Domiguez-Vazquez, A.; Ruvalcaba-Macias, A. M.; Lugo-Pfeiffer, C.; Mackenzie, C. D.; Beltran F. Chemotherapy of onchocerciasis: a controlled comparison of mebendazole, levamisole, and diethylcarbamazine. Lancet, 1981; 2: 485-90.

.

101. Awadzi, K.; Schulz-Key, H.; Howells, R. E.; Haddock, D. R. W.; Gilles, H. M. The chemotherapy of onchocerciasis VIII Levamisole and its combination with the benzimidazole. Ann Trop Med Parasitol, 1982; 76(4): 459-73.
102. Lacey, E. Mode of action of benzimidazoles Parasitol Today, 1990; 6:112.
103. (a) Rossignol, J. F.; Maisonneuve, H. Albendazole: a new concept in the control of intestinal helminthiasis. Gastroenterol Clin Biol, 1984; 8: 569. (b) Oxberry, M. E.; Geary, T. G and Prichard, R. K. Assessment of benzimidazole binding to individual recombinant tubulin isotypes from Haemonchus contortus. Parasitol, 2001; 122: 683.
104. (a) Addiss, D. G.; Louis-Charles, J. Am J Trop Med Hyg, 1997; 57: S215. (b) Addiss, D. G.; Beach, M. J.; Streit, T. G.; Lutwick, S.; LeConte, F. H.; Lafontant, J. G.; Hightower, A. W.; Lammie, P. J. Randomised placebo-controlled comparison of ivermectin and albendazole alone and in combination for Wuchereria bancrofti microfilaraemia in Haitian children. Lancet, 1997; 350: 480.

105. (a) Ottesen, E. A.; Ismail, M. M.; Horton, J. The role of albendazole in programmes to eliminate lymphatic filariasis. Parasitol Today, 1999; 15: 382. (b) Harder A. Chemotherapeutic approaches to nematodes: current knowledge and outlook. Parasitol Res. 2002 ;88(3):272-7.

106. Sorenson, E.; Ismail, M.; Amarasinghe, D. K.; Hettiarachchi, I. The efficacy of three anthelmintic drugs given in a single dose. Ceylon Med J CSIR Lanka, 1996; 41: 42.

107. Reddy, A. B.; Rao, U. R.; Chandrashekar, R.; Shrivastava, R.; Subrahmanyam, D. Comparative efficacy of some benzimidazoles and amoscanate (Go.9333) against experimental filarial infections. Tropenmed Parasitol. 1983 Dec;34(4):259-62.

108. Roos, M, H. The role of drugs in the control of parasitic nematode infections: must we do without? Parasitol, 1997; 114: S137.

109. Harder, A. In: Mehlhorn H (ed) Encyclopedic references of parasitol, 2nd edn. Springer, Berlin Heidelberg New York, 2000, 213.

110. Awadzi, K.; Gilles, H. M. The chemotherapy of onchocerciasis IV further trials with metrifonate. Ann Trop Med Parasitol, 1980; 74(3): 355-62.

111. Fuglsang, H.; Anderson, J. Effects of a single dose of metrifonate on the forest strain of Onchocerca volvulus in Cameroon. Trop med Parasitol, 1977; 28: 439.

112. Bockaire, M. J.; Alexander, N. D. E.; Hyun, P.; Dimber, Z.; Bockaire, F.; Ibam, E. Randomised community-based trial of annual single-dose diethylcarbamazine with or without ivermectin against Wuchereria bancrofti infection in human beings and mosquitoes. Lancet, 1998; 351: 162-8.

113. Moulia-Pelat, J. P.; Glaziou, P. H.; Weil, G. J.; Nguyen, L. N.; Gaxotte, P. H.; Nicolas, L. Combination ivermectin plus diethylcarbamazine, a new effective tool for control of lymphatic filariasis.Trop Med Parasitol, 1995; 46: 9-12.

114. Ismail, M, M.; Jayakody, R. L.; Weil, G. J.; Nirmalan, N.; Jayasinghe, K. S. A.; Abeyewickrema, W.; Rezvi Sheriff, M. H.; Rajaratnam, H. N.; Amarasekera, N.; de Silva, D. C. L.; Michalski, M. L.; Dissanaike, A. S. Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. Trans R Soc Trop Med Hyg, 1998; 92: 94.

115. Nicolas, L.; Plichart, C.; Nguyen, N. L.; Moulia-Pelat, J. P. Reduction of Wuchereria bancrofti adult worm circulating antigen after annual treatments of diethylcarbamazine combined with ivermectin in French Polynesia. J Inf Dis, 1997; 175: 489.

116. Plaisier, A. P. et al. Effectiveness of annual ivermectin treatment for Wuchereria bancrofti infection. Parasitol Today, 2000; 16: 298.

117. Ottenson, E. A.; Ismail, M. M.; Hortan, J. The role of albendazole in programmes to eliminate lymphatic filariasis. *Parasitol. Today*, **1999**, *15*, 382.

.

118. Fatma, N.; Sharma, S.; Chatterjee, R.K. 2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl ketone--a new antifilarial agent. Acta Trop. 1989 ;46(5-6):311-21.

119. Abuzar, S.; Sharma, S.; Fatma, N.; Gupta, S.; Murthy, P. K.; Katiyar, J. C.; Chatterjee, R. K.; Sen, A.B. Studies in potential filaricides .18 . synthesis of 2,2'-disubstituted 5,5'-dibenzimidazolyl ketones and related compounds as potential anthelmintics. J Med Chem, 1986; 29(7): 1296-9.

120. Dubey, R.; Abuzar, S.; Sharma, S.; Chatterjee, R. K.; Katiyar, J. C. Synthesis and anthelmintic activity of 5(6) – (benzimidazol -2- yl carbamoyl) and (4- substituted piperazin -1- yl) J Med Chem, 1985; 28(11): 1748-50.

121. Ram, S.; Skinner, M.; Kalvin, D.; Wise, D. S.; Townsend, L. B.; McCall, J. W.; Worth, D.; Ortwine, D.; Werbel, L. M. . Synthesis of potential antifilarial agents. 1-(5-Benzoylbenzimidazol-2-yl)-3-alkyl- and -arylureas J Med Chem, 1984; 27(7):914-917.

122. Ram, S.; Wise, D. S.; Wotring, L. L.; McCall, J. W.; Townsend, L. B. Synthesis and biological activity of certain alkyl 5 – (alkoxycarbonyl) -1H- benzimidazole -2- carbamates and related derivatives a new class of potential antineoplastics and antifilarial agents. J Med Chem, 1992; 35(3); 539-47.

123. (a) Pani, S. P.; Subramanyam Reddy, G.; Das, L. K.; Vanamail, P.; Hoti, S. L.; Ramesh, J . Das, P. K. Tolerability and efficacy of single dose albendazole, diethylcarbamazine citrate (DEC) or co-administration of albendazole with DEC in the clearance of *Wuchereria bancrofti* in asymptomatic microfilaraemic volunteers in Pondicherry, South India: a hospital-based study Filaria Journal, 2002; 1; 1. (b) Casley-

Smith.; Jamal, J. R.; Casley-Smith. S. J. R. Reduction of filaritic lymphoedema and elephantiasis by 5,6 benzo-alpha-pyrone (coumarin), and the effects of diethylcarbamazine (DEC). Ann Trop Med Parasitol, 1993; 87; 247.

124. Srivastava, A. K.; Tripathi, R. P.; Khan, A. R.; Bhaduri, A. P.; Singh, S. N.; Chatterjee, R. K. Glutathione-s-Transferase activity in setaria cervi females and effect of new antifilarial compounds. Indian J Parasitol, 1994; 18: 127.

125. Tripathi, R. P.; Tripathi, R.; Bhaduri, A. P.; Singh, S. N.; Chatterjee, R. K.; Murthy, P. K. Antifilarial activity of some 2H-1-benzopyran-2-ones (coumarins). Acta Trop, 2000; 76: 101.

126. Tripathi, R. P.; Tewari, V. K.; Bhattacharya, S.; Tyagi, K.; Srivastava, V. M. L.; Murthy, P. K. 7-O-[4-methyl piperazine-1-(2-acetyl)]-2H-1-benzopyran-2-one: a novel antifilarial lead compound. Acta Trop, 2003; 87: 215.

127. Katiyar, D.; Tewari, V. K.; Tripathi, R. P.; Reddy, V. M.; Bhattacharya, S. M.; Saxena, J. K. Synthesis and antifilarial evaluation of 7-O-acetamidyl-4-alkyl-2H-1-benzopyran-2-ones. Arzneim-Forsch/Drug Res. 2003; 53; 857.

128. Bhattacharya, S.; Katiyar, D.; Bajpai, P.; Tripathi, R. P.; Saxena, J. K. 4-Methyl-7-(tetradecanoyl)-2H-1-benzopyran-2-one: a novel DNA topoisomerase II inhibitor with adulticidal and embryostatic activity against sub-periodic Brugia malayi. Parasitol Res, 2004; 92: 177.

129. (a) Bose, C.; Agarwal, S. K.; Chatterjee, R. K.; Srivastava, V. M. L.. Carboline antifilarials: effects on carbohydrate metabolising enzymes in Litomosoides carinii female. Indian J Exp Biol. 1994 ;32(6):431-3. (b) Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S. Antiparasitic agents part x – synthesis of disubstituted-1,6-dihydropyrido[3,4-b]imidazo[4,5-e]indoles asanthelmintic agents. Indian J Chem, 1990; 29B: 843. (c) Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S.; Gupta, S.; Katiyar, J. C. Antiparasitic Agents: part XIX- synthesis and anthelmintic activity of 6- and 8-(2,4-dioxoquinazolin-3-yl)-1-substituted-9H-pyrido-[3,4-b]indoles, 6-and 8-(2-methyl-5-acetamidobenzimidazol-1-yl)-1-substituted-9H-pyrido[3,4-b]indoles and6-[2-carbomethoxyamino-5-(N,N´-dicarbomethoxyguanido)benzimidazol-1-yl]-1-phenyl-9H-pyrido[3,4-b]indole.Indian J Chem, 1990; 29B: 848.

130. (a) Kumar, P.; Agarwal, S. K.; Bhakuni, D. S. Antiparasitic agents: part XI – synthesis and anthelmintic activity of 6-/8-(2-carbomethoxyamino) benzimidazole]-5-

carbonulamin-1-substituted-9H-pyrido[3,4-b]indoles. Indian J Chem, 1990; 29B: 1077. (b) Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S.; Singh, S. N.; Chatterjee, R. K. Z. Naturforsch, 1994; 49: 526. Antiparasitic agents: part XVI- synthesis of 5(c)-substituted benzimidazole-2-carbamates as anthelmintic agents. Indian J Chem, 1993; 32B:453.

131. (a) Kapoor, S.; Singhal, K. C. 5/6/7/8 mono or disubstituted 1H/1-phenyl-9H-pyrido [3,4 b] indoles--a new class of antifilarial agents and their relationship with voltage sensitive calcium channels in Setaria cervi. Indian J Exp Biol. 1998; 36(9):887-90. (b) Agarwal, A.; Agarwal, S. K.; Singh S. N.; Fatima N.; Chatterjee, R. K. Structure-antifilarial activity relationship of 5/6/7/8-mono- or disubstituted 1H/1-phenyl-9H-pyrido[3,4-b]indoles--a new class of potential filaricides (c) Agarwal, A.; Agarwal, S. K. Antiparasitic agent; part XVII- synthesis of 2- methyl mercapto-7-H/phenyl-1H,6H-pyrido[3,4-b]imidazo[4,5-e]indoles, 6-/8-(4-oxo-2-thioquinazolin-3-yl)-1-H/phenyl-9H-pyrido[3,4-b]indoles and 6-/8-(2,4-dioxo-1,3-benzoxazin-3-yl)-1-phenyl-9H-pyrido[3,4-b]indoles as anthelmintic agents. Indian J Chem, 1995; 34B: 323.

132. (a) Srivastava, S.; Agarwal, A.; Chauhan, P. M. S. Potent 1,3-disubstituted-9H-pyrido[3,4-b]indoles as new lead compounds in antifilarial chemotherapy. J Med Chem, 1999; 42; 1667. (b) Srivastava, S K.; Agarwal, A.; Chauhan, P. M. S.; Agarwal, S. K.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. Potent 1,3-disubstituted-9H-pyrido[3,4-b]indoles as new lead compounds in antifilarial chemotherapy. Bioorg Med Chem, 1999; 7: 1223.

133. Sundberg, R. J.; Biswas, S.; Murthi, K. ; Rowe, D.; McCall, J. W.; Dzimianski, M. T. Biscationic heteroaromatics as microfilaricides : Synthesis of bisamidine and bisguanyl – hydrazone derivatives of substituted imidazo [1,2-a] pyridines. J Med Chem, 1998; 41(22); 4317-28.

134. Kumar, Y.; Green, R.; Wise, D. S.; Wotring, L. L.; Townsend, L. B. Synthesis of 2,4 disubstituted thiazoles and selenazoles as potential antifilarial and antitumor agents.2,2 – Arylamido and 2 alkylamido derivatives of 2- amino -4-(isothiocyanato methyl) thiazole and 2- amino -4- (isothiocyanatomethyl) selenazole. J Med Chem, 1993; 36(24);3849-52.

135. Kumar, Y.; Green, R.; Borysko, K. Z.; Wise, D. S.; Wotring, L. L.; Townsend, L. B. Synthesis of 2,4 disubstituted thiazole and selenazoles as potential antitumor and antifilarial agents : 1 Methyl 4 -(isothiocyanatomethyl) thiazole -2- carbamates selenazole -2- carbamates and related derivatives. J Med Chem, 1993; 36(24): 3843-8.

136. Srivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P.; Fatima, N.; Chatterjee, R. K. Quinolones : Novel probes in antifilarial chemotherapy. J Med Chem, 2000; 43(11): 2275-9.

137. Srivastava, S.; Haq, W.; Murthy, P. K.; Chauhan, P. M. Solid phase synthesis of quinolones. Bioorg Med Chem Lett, 1999; 9; 1885.

138. Srivastava, S. K.; Chauhan, P. M.; Agarwal, S. K.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. Syntheses and antifilarial profile of 5-amino and 5,8-diamino-isoquinoline derivatives: A new class of antifilarial agents Bioorg Med Chem Lett, 1996; 6: 2623.

139. Tewari, S.; Chauhan, P. M.; Bhaduri, A. P.; Fatima, N.; Chatterjee, R. K. Synthesis and antifilarial profile of 7-chloro-4-(substituted amino) quinolines: a new class of antifilarial agents. Bioorg Med Chem Lett, 2000; 10; 1409.

140. Tewari, S.; Chauhan, P. M.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. 1,1′-Dicyano-2-substituted ethylenes: A new class of glucose uptake inhibitors in antifilarial chemotherapy. Bioorg Med Chem Lett, 1997; 7; 1891.

141. Chauhan, P. M.; Singh, S. N.; Chatterjee, R. K. Antifilarial profile of substituted pyrazoles: A new class of antifilarial agents. Indian J chem, 1993; 32B: 858.

142. Chauhan, P. M.; Chatterjee, R. K. Synthesis of 1,3-substitutted indoles, 2,4,6-substituted-s-triazines and 4,5-substituted pyrazoles as possible antifilarial agents. Indian J chem, 1994; 33B: 32.

143. Srivastava, S.; Chauhan, P. M.; Bhaduri, A. P.; Murthy, P. K.; Chatterjee, R. K. Secondary amines as new pharmacophores for macrofilaricidal drug design. Bioorg Med Chem Lett, 2000; 10: 313.

144. Brienne, M. J.; Varech, D.; Leclercq, M.; Jacques, J.; Radembino, N.; Dessalles, M. C.; Mahuzier, G.; Gueyouche, C.; Bories, C.; Loiseau, P. New antifilarial agents .I. Epoxysulphonamide and ethylene sulphonamides. J Med Chem, 1987; 30: 2232-9.

145. Radembino, N.; Loiseau, P. M.; Dessalles, M. C.; Marchat, L.; Bories, C.; Gayral, P.; Mahuzier, G. Epoxyethane-/ethynesulfonamides with antifilarial activities. Degradation kinetics and inhibitory effect on filarial malate dehydrogenase and lactate dehydrogenase. Arzneim-Forsch/Drug Res, 1998; 48: 294.

146. (a) Srivastava, A. K.; Tripathi, R. P.; Khan, A. R.; Bhaduri, A.P.; Singh, S. N.; Chatterjee, R. K. Indian J Parasitol, 1994; 18: 127.

147. Srivastava, A.K.; Tripathi, R. P.; Khan, A. R.; Bhaduri, A. P. Effect of 3-*O*-(aminoalkyl)- α-D-gluco (xylo) furanoses on glutathione metabolism of falarial parasites. Helminthol, 1995; 32: 25.

148. Khan, A. R.; Tripathi, R. P.; Bhaduri, A. P.; Sahai, R.; Puri, A.; Tripathi, L. M.; Srivastava, V. M. L. Synthesis and immunomodulatory activity of 3-O-[2'-hydroxy-3'-N,N-disubstituted aminopropan-1'-yl]-alpha-D-glucofuranoses. Eur J Med Chem, 2001; 36; 435.

149. Tripathi, R. P.; Rastogi, S. K.; Kundu, B.; Saxena, J. K.; Reddy, V. J. M.; Srivastava, S.; Chandra, S.; Bhaduri, A. P. Identification of inhibitors of DNA topoisomerase II from a synthetic library of glycoconjugates. Combinatorial Chem High Throughput Screen, 2001; 4: 237.

150. Khan, A. R.; Tripathi, R. P.; Tiwari, V. K.; Mishra, R. C.; Reddy, V. J. M.; Saxena, J. K. Conjugate Addition of Amines to Sugar Derived Olefinic Ester: Synthesis of Glycosylated Amino Esters as DNA Topoisomerase –II Inhibitors. J. Carbohydr. Chem, 2002; 21 (6): 591.

151. Verma, R. S.; Shukla, A.; Chatterjee, R. K. . Evaluation of vanillic acid analogues as a new class of antifilarial agents. Indian J Exp Biol, 1993; 31(10): 819.

152. Loiseau, P. M.; Depreux, P. Invivo antifilarial evaluation of phenoxycyclohexane derivatives. Ann Trop Med Parasitol, 1993; 87: 469-76.

153. (a) Loiseau, P. M.; Jaffe, J. J.; Craciunescu, D, G. In vitro antifilarial activity of organometallic complexes against infective larvae of Molinema dessetae and adult females of Brugia pahangi. Int J Parasitol, 1998; 28; 1279. (b) Loiseau, P. M.; Lubert, P.; Wolf, J. G. Synthesis and in vitro anthelmintic properties of some new dithiaarsanes. Arzneim-Forsch/Drug Res, 1999; 49: 944.

154. Tagboto, S. K.; Townson, S. *Onchocera volvulus* and *O. lienalis* : The micofiracidal activity of moxidectin compared with that of invermectin invitro invivo. Ann Trop Med Parasitol, 1996; 90: 497-505.

155. Singh, S. N.; Bhatnagar, S.; Fatma, N.; Chauhan, P. M. S.; Chatterjee, R. K. Antifilarial activity of a synthetic marine alkaloid, aplysinopsin (CDRI Compound 92/138). Trop Med Int Health, 1997; 2: 535.

156. Loiseau, P. M.; Bourass, J.; Letourneux, Y. Lymphotropic antifilarial agents derived from closantel and chlorambucil. Int J Parasitol, 1997; 27: 443.

157. Elkihel, L.; Loiseau, P. M.; Bourass, J.; Gayral, P.; Letourneux, Y. Synthesis and orally macrofilaricidal evaluation of niclosamide lymphotropic prodrugs. Arzneim-Forsch/Drug Res, 1994; 44(11): 1259.