SUMMARY
Introduction

The increasing understanding of the disease processes and their treatment has made man able to control a large number of diseases. The recent proclamation of the World Health Organisation 'health for all by 2000 A.D.' is a testimony of this fact that a large variety of human diseases have been controlled and those which have not been eradicated till now will be eliminated in the near future because of the various newer approaches introduced in the control of human diseases. The provision of health for all by 2000 A.D. may come live for a number of diseases but does not seem likely in the case of parasitic diseases, specially helminth infestations which even today invade several hundred million people around the world. This is primarily because of the fact that the helminth infestations are chiefly prevalent in those areas of the tropics where there is poor health education and those who know something about tropical diseases are unable to prevent themselves to the risk of infection due to several reasons, such as environmental, occupational, economical and lack of medical facilities. These facts underscore the need to develop broad-spectrum anthelmintics with low toxicity.
which should be cheap and could be afforded by poor masses.

A large variety of chemotherapeutic agents have been introduced which may be used successfully to treat a variety of helminth infections \([1,2]\). However, there is still a need to develop anthelmintics which can be used to treat various types of intestinal helminths, since mixed infestation is a common concurrence in endemic areas. In the case of tissue dwelling parasites such as filarial worms, we need a drug having efficacy against different stages of its development. The present thesis is directed towards developing suitable drugs for two of the important helminth diseases, hookworm infestations and filariasis, both prevalent in India and in other large areas of the tropics.

**Synthesis of Potential Antihookworm Agents**

Hookworm disease primarily affects field workers and has a detrimental effect on the general health and working capacity of the victims \([3]\). The presence of hookworm parasites in sheep, goats, pigs, poultry and cattle greatly affects the production of milk, meat and wool in the agriculture based countries of the world.

One of the recent developments in the chemotherapy of hookworm diseases is the demonstration of powerful anthelmintic activity associated in a variety of benzimi-
Diazoles derived from 2,5-disubstituted benzimidazoles [4]. The compounds belonging to this series have been shown to possess broad spectrum of anthelmintic activity against both the helminths living in elementary canal and connective tissues of the host. Although a number of drugs such as thiabendazole, mebendazole and fenbendazole have emerged as broad-spectrum human anthelmintics, a detail structure activity relationship is yet to come out in this class of compounds. Keeping these facts in view it was considered pertinent to synthesize a variety of 2,5-disubstituted benzimidazoles with the aim to develop suitable antihookworm agents as also to delineate minimal structure requirements in 2,5-disubstituted benzimidazoles for this activity. Thus, the synthesis of 2-substituted arylaminomethyl and 1-arylbenzimidazoles (2, 4-6) was carried out [5,6]. The synthesis of 2 was achieved by condensing 2-chloromethylbenzimidazole (1) with different arylamines while 1-arylbenzimidazoles (4) were obtained by cyclising the corresponding N-aryl-α-phenylenediamines (3) with different cyclising agents. Further reaction of the 4 with arylisothiocyanates and thiophosgene led to the formation of other 1-arylbenzimidazoles (5, 6).
1. $\text{Ar-NH}_2 \xrightarrow{} \text{Cl, OCH}_3, \text{NHCOCH}_3, \text{NH}_2, \text{NCS, OAr etc.}$

2. $\text{R = Cl, OCH}_3, \text{NHCOCH}_3, \text{NH}_2, \text{NCS, OAr etc.}$

3. Cyclisation

4. $\text{R = H, CH}_3, \text{OH}$
   $\text{R}^1 = \text{NHCOCH}_3, \text{NH}_2$
   1. Reduction or $\text{H}^+$
   2. $\text{CSCl}_2$

5. $\text{R = H, CH}_3, \text{OH}$
   $\text{R}^1 = \text{NO}_2, \text{NH}_2, \text{NCS}$
   $\text{R}^2 = \text{NH}_2, \text{NCS}$

6. $\text{R = H, CH}_3, \text{OH}$
   $\text{R}^1 = \text{H, Cl}$
A number of 2-substituted 5(6)-arylamino benzimidazoles (8-10) [7] have also been synthesized starting with 4-arylamino-2-phenylenediamines (7). Reaction of 4-nicotinoylamino-2-phenylenediamine with trifluoroacetic acid gave 2-trifluoromethyl-5(6)-nicotinoyliminobenzimidazole (8) while alkyl 5(6)-arylaminobenzimidazole-2-carbamates (2) were prepared by cyclising the diamines with 1,3-dicarbal-koxy-5-methylisothiureas. The diamines were also allowed

\[
\begin{align*}
\text{1. 4-Nitrobenzaldehyde} & \quad \text{2. Ra-Ni, H}_2 \\
& \quad \text{3. C}_6\text{H}_5\text{S-C=OOR} \\
\text{NH} & \quad \text{NHCOOR} \\
\text{Ar} & \quad \text{N} \\
\text{NH} & \quad \text{Ar} \quad \text{NHCOOR} \\
\text{O} & \quad \text{O} \\
\text{Ar} & \quad \text{Ar} \\
\end{align*}
\]

\[
\begin{align*}
2. \text{ } R = \text{CH}_3, \text{ C}_2\text{H}_5 \\
\text{Ar} = \text{Various substituted phenyls, 2-furyl, 3-pyridyl} \\
\end{align*}
\]

\[
\begin{align*}
10. \text{ } R = \text{NO}_2, \text{ NH}_2, \text{ NCS} \\
\text{Ar} = \text{Various substituted phenyls, 3-pyridyl} \\
\end{align*}
\]
to react with 4-nitrobenzaldehyde to give corresponding 5(6)-arylamino-2-arylbenzimidazoles which were reduced and treated with thiophosgene to yield corresponding isothiocyanates (10).

Based on the potent anthelmintic activity of fenbendazole and 2-arylthio- and sulphonobenzimidazoles [8,9], the synthesis of 2-alkylthio-/sulphonobenzimidazoles (12-14) was carried out [10] starting with benzimidazole-2-thiols as shown below.

\[
\begin{align*}
11, & \quad R = H, NO_2 \\
12, & \quad R = \text{Alkyls} \\
13 & \quad R = \text{Alkyls} \\
14, & \quad R = NH_2, \text{NCS} \\
& \quad R^1 = \text{Alkyls} \\
& \quad X = S, SO_2
\end{align*}
\]
The preparation of 5(6)-(benzimidazol-2-ylthio/sulphono)benzimidazoles (17, 18) [10] was carried out by the cyclisation of corresponding diamines with alkyl carboxylic acids and 1,3-dicarbalkoxy-S-methylisothioureas.

![Reaction Scheme]

15. \( R = H, Cl \)

16. \( R = H, Cl \)

1. Ra-Ni, \( H_2 \)
2. Cyclisation

1. Ra-Ni, \( H_2 \)
2. \( CH_3S-C\equivNCOOC_2H_5 \)

17. \( R = H, Cl \)
\( R^1 = H, CH_3, NHCOOCH_3, NHCOOC_2H_5 \)

18. \( R = H, Cl \)
\( R^1 = CH_3, C_2H_5 \)
The powerful anthelmintic activity exhibited by mebendazole led to the synthesis of some of its structural analogs (22) starting with 4-chloro-4'-hydroxy-3-nitrobenzophenone (19) by the scheme shown below [11].

\[
\begin{align*}
\text{1. } & \text{NH}_3 \\
\text{2. } & \text{Ra-Ni, } \text{H}_2 \\
\text{R} & = \text{H, } \text{CH}_3, \text{OH, } \text{NHCOO}_2\text{H}_5
\end{align*}
\]
During the above course of work the substitution reaction of nitroaryl chlorides in DMF was reinvestigated. It was observed that activated aryl halides when refluxed with DMF in presence of bases like ethanolamine or propylamine gave rise to the exclusive formation of the corresponding N,N-dimethylamino derivatives (24). It was also observed that cyclisation of the 1,2-aryldiamines with 1,3-dicarbalkoxy-S-methylisothioureas in technical grade DMF does not yield the corresponding alkyl benzimidazole-2-carbamates (26), instead benzimidazol-2-ones (29) were obtained in high yields [12]. The probable mechanism of this reaction has also been investigated.

\[
\begin{align*}
\text{Primary aliphatic amine} & \quad \xrightarrow{\text{DMF}} \\
\text{23, } R = H, \text{NH}_2, \text{NHCOCH}_3 & \quad \text{24, } R = H, \text{NH}_2, \text{NHCOCH}_3
\end{align*}
\]
Filariasis, another major helminth disease, is prevalent in several states of India affecting nearly 18 million people. It is estimated that nearly 400 million people are the victims of this disease suffering from various disabling effects of the infection such as enlargement of arms, limbs, breasts and genitals. In addition, the disease due to *O. volvulus* and *Loa loa*, endemic chiefly in African continent, is responsible for river blindness and painful Calabar swellings. Filariasis, thus, poses
a major public health problem because of the logistic difficulties associated with its treatment. The main bottleneck of the chemotherapy of filariasis is the non-availability of a suitable drug which can be used to eliminate microfilariae and adult worms. The use of diethylcarbamazine has its value only in suppression or temporary cure of the disease due to its selective action on the microfilarial stage of the parasites. As regards its efficacy against adult worms there are conflicting views [13].

It is, therefore, of utmost importance to explore the chemotherapeutic value of other organic molecules which may be further used as prototype molecules in searching better filaricides. Furthermore, it is equally valuable to synthesize other piperazines carrying the pharmacophores with proven anthelmintic efficacy [14]. Bearing these facts in view, a series of 1,4-disubstituted piperazines (30-37) [15] have been carried out which is described in the II chapter of the thesis.
Cl

Cl

(~\text{Ar=})

different substituted phenyls

R = \text{NO}_2, \text{NCS}

X = 0, S

N = Various secondary amines

32, Ar = different substituted phenyls

33, R = \text{NO}_2, \text{NCS}

X = 0, S

N = Various secondary amines
Various amines

\[ \text{R} = \text{N(C}_2\text{H}_5)_2, \text{OC}_2\text{H}_5, \text{OCH}_2\text{CH(CH}_3)_2 \]
\[ \text{N} = \text{NH}_2, \text{N}-\text{CH}_3, \text{N} \]

\[ \text{R} - \text{C - N - CH}_2\text{-N - R}^1 \]

\[ \text{R} = \text{N(C}_2\text{H}_5)_2, \text{OCH}_2\text{CH(CH}_3)_2 \]
\[ \text{R}^1 = \text{CON(C}_2\text{H}_5)_2, \text{CH}_3 \]

\[ \text{R} = \text{Cl, Br} \]
\[ \text{R}^1 = \text{H, Br} \]
\[ \text{R}^2 = \text{H, Cl} \]
\[ \text{R}^3 = \text{NO}_2, \text{NH}_2, \text{NCS} \]
The synthesis of some amodiaquine analogs (38) has been carried out by the Mannich reaction of 4-(4-hydroxyphenyl)aminoquinazolines with various amines in presence of formaldehyde [16].

While searching for a new type of prototype molecule, the synthesis of alkyl 4(5)-alkyl/arylimidazoline-2-carbamates (39) was carried out by the cyclisation of corresponding 1-alkyl/arylethylenediamines with 1,3-dicarbalkoxy-S-methylisothioureas. One of such compounds, 39 (R = H, R\textsuperscript{1} = C\textsubscript{2}H\textsubscript{5}) showed marked activity against experimental filariasis.

\[\text{38, } R = \text{H, Cl} \quad \text{39, } R = \text{H, CH}\textsubscript{3}, \text{aryls} \]

\[N = \text{different secondary amines} \quad R^1 = \text{H, CH}\textsubscript{3}, \text{C}_2\text{H}_5 \]

3-Ethyl-8-methyl-1,3,8-triazabicyclo[4,4,0]decan-2-one (Centperazine, 40) [17], a rigid analog of diethylcarbamazine, developed in this Institute, has been shown
to possess promising activity against human filariasis. Attempts to arrive at an economically feasible and convenient synthesis of this drug have been made and described in the thesis.

\[
\begin{array}{c}
\text{C}_2\text{H}_5 \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{CH}_3 \\
40
\end{array}
\]

The present work has yielded a few compounds which show appreciable activity against the hookworms, \textit{A. ceylanicum} and \textit{N. brasiiliensis} and tapeworms, \textit{H. nana} in laboratory animals. Some of the compounds have also shown micro- and macrofilaricidal activity against \textit{I. carinii} and \textit{B. malayi} in experimental animals. A number of compounds have also been submitted for their antimicrobial activity and the results are reported.
References


