SYNTHETIC AND NATURALLY OCCURRING BIOLOGICALLY ACTIVE COMPOUNDS

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The main aim of the thesis is to mimic the biological system through the basic organic molecules synthesized under this research project and the development of new antiamoebic drugs and their ability to build host resistance against reinfection with parasite, *Entamoeba histolytica*. Amoebiasis is an ubiquitous disease particularly in areas of Asia, Africa and South America, where it is endemic and is responsible for 100,000 deaths worldwide and is the second leading cause of death due to parasitic disease. At date, the ideal treatment for amoebiasis does not exist. The drugs used currently for the treatment of amoebiasis include agents that are mutagenic in bacteria, carcinogenic to laboratory rodents (metronidazole), cardiotoxic for human (emetine) and have been associated with transient myopia, neuropathy and immunosupression. Because of their toxicity it is desirable, therefore, to find new amoebicides for a greater margin of safety and have amoebicidal activity with less toxicity for the host. In addition, the possibility of further development of resistant strain, as well demonstrated by other protozoa, cannot be excluded.

Thiosemicarbazones, a class of compounds possessing a wide spectrum of medicinal properties, have been studied for activity against tuberculosis, leprosy, bacterial and viral infections, psoriasis, rheumatism, trypanosomiasis and coccidiodis. In past few years thiosemicarbazones derived from 2-formylpyridine and related aldehydes have been of great interest because of their reported antineoplastic action.

Part one of the thesis deals with the synthesis of dithiocarbazates, benzimidazole and heterocyclic thiosemicarbazones derivatives attracted our attention because they showed activity in our primary screening. It was decided to exploit this interest led by ascertaining the molecular features essential for activity and utilizing them to develop a new class of antiamoebic agents. Twenty-nine compounds were synthesized belonging to dithiocarbazates, benzimidazole derivatives and thiosemicarbazones to screen for antiamoebic activity. Out of these, S-benzyldithiocarbazate of 2-acetylpyridine showed comparable activity with the standard drug (metronidazole).

Thiosemicarbazones were prepared by simple process in which N^4-thiosemicarbazone moiety was replaced by aliphatic, arylic and cyclic amines. Literature survey revealed that the presence of certain bulky groups at N^4 of the thiosemicarbazone moiety greatly enhances biological activity.

Part two describes the incorporation of transition metals into the molecular structure of

potentially active dithiocarbazates, benzimidazole and thiosemicarbazones derivatives. All the dithiocarbazates and thiosemicarbazones behave as bidentate ligand by coordinating through azomethine nitrogen and thionic sulphur whereas benzimidazoles coordinate through nitrogen and hydroxyl oxygen / nitrogen. Metal ions are known to accelerate drug action and the efficacy of therapeutic agent enhanced upon the coordination with metal ion. A novel strategy for the development of alternative therapies against tropical diseases, based on the modification of known antiprotozoal drug (metronidazole) through the incorporation of a transition metal and report very encouraging results better than metronidazole.

These metal complexes of metronidazole were subjected to DNA binding studies with calf thymus DNA. It has been shown that transition metal complexes can interact noncovalently with nucleic acid by intercalation groove binding or external electrostatic binding and reduce the toxicity of the drug. The effect of binding of potent compounds was determined by electronic absorption spectroscopy.

Part three emphasizes on plants species, which are being used in traditional medicine to treat dysentery; these plants should be analyzed to determine their efficacy (and toxicity) and thus their potential as source of new antiamoebic agents. These plants include species of the family Bignoniaceae, e.g. *Kigelia pinnata* and Asclepiadaceae, e.g. *Calotropis gigantea*, which have long been used in the treatment of dysentery. To achieve this goal, plants extracts were prepared and biologically monitored fractions were undertaken for detailed studies. Four known compounds were isolated, purified and characterized by comparing their spectral data with published literature values.

Part four presents the assessment of i*n vitro* activity of dithiocarbazates, benzimidazole, thiosemicarbazones derivatives and their metal complexes with palladium, platinum, ruthenium, gold, copper, vanadium, molybdenum and tungsten against *Entamoeba histolytica* (strain HK-9 and HM1:1MSS)*, Giardia lamblia* (strain IMSS-0989) and *Trichomonas vaginalis* (strain tv-43). All the antiamoebic experiments were carried out by microdilution method. The test was also performed to detect antiamoebic activities of plant extracts prepared from the traditional remedies *Kigelia pinnata* stem bark and *Calotropis gigantea* root bark. Four known compounds from these plants were tested *in vitro* against *Entamoeba histolytica* and found active, but verminoside showed better activity than the standard drug. The percent inhibition of amoebal growth of all compounds, synthetic as well as naturally occurring was calculated from the optical densities of the control and test wells and was plotted against the logarithm of the dose of the drug or extract being tested. Although metronidazole is an effective antiamoebic medication but it has serious side effects. Metal complexes of metronidazole were tested *in vitro* and showed promising results. The metronidazole metal complexes were screened for *in vivo* antiamoebic activity (animal model, golden hamsters). Hamsters with experimental amoebic hepatic abscess were fed metronidazole complexes for 5 or 10 days. It was found that metronidazole complexes are more efficacious and less toxic antiamoebic agent than metronidazole.