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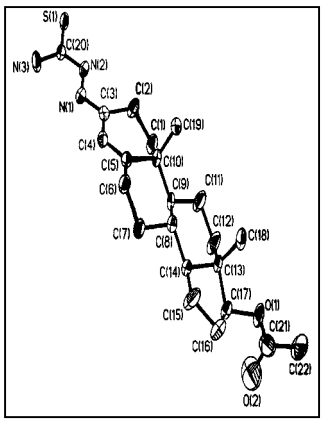
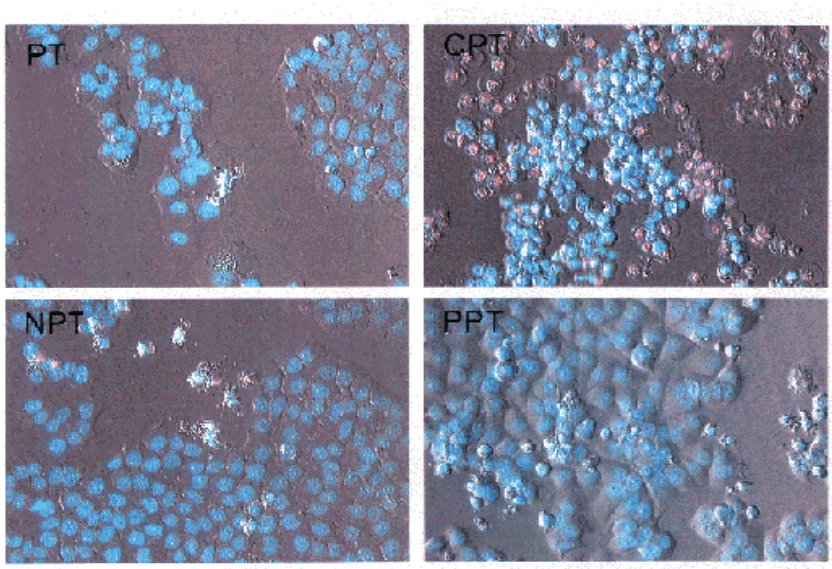
CURRENT RESEARCH INTERESTS :

The thrust of research work in our group is directed towards designing drugs for hormone-responsive cancers, colon cancers, tuberculosis and malaria which is based on the principles of molecular recognition through synthetic constructs or carrier-mediated drug targeting. The work is an extension of our earlier experience in biomimetic chemistry of metalloenzymes involved in oxygen evolution and its activation. We believe that role of metal ions as revealed by recent discoveries in biological processes such as protein conformations and activations, control of enzyme active sites, molecular recognition through cell surface receptors, signal transduction processes leading to apoptosis or drug resistances are challenging areas for interdisciplinary researches. With this in mind we have established some of the bioassay facilities in our own lab while for specialized assays we have maintained close associations with leading international researchers in the respective fields. The outline of some of the research projects presently carried out in our lab is listed below.

1. Drug Design for Hormone Responsive Cancers:

The over-expression of steroid hormone receptors in malignant cells of breasts, ovaries and prostate offer excellent opportunities for their selective targeting through covalent attachments of cytotoxic drugs with corresponding hormone molecules or their mimics. The cytotoxic agents that have so far been linked in such a manner include nitrosoureas, nitrogen mustards, epoxides, aziridines and DNA intercalators. Work in our laboratory is directed towards modifying (not necessarily enhancing) the binding characteristic of the estrogenic moiety in order to conjugate it with selected metal ions having cytotoxic pharmacophores as ligands. The overall greater lipophillic nature of these conjugates facilitates their cellular internalization while eventual intracellular dissociation of these conjugates deposits the cytotoxic pharmcophore and the selected metal ions in the cytoplasmic fluid resulting in a multitude of antiproliferative actions in the malignant cells. In this way we have been able to design drug molecules which are effective against ER positive and ER negative cells as well as drug resistant cancer cells with minimal damages to the normal cells. Their structures are being refined for the optimum activity. For the estrogen independent cancers similar strategy is used employing flavonoid moities as the basic structural scaffold and appropriate pharmacophores are built upon it. The resulting compounds are proving to be effective AKT inhibitors.



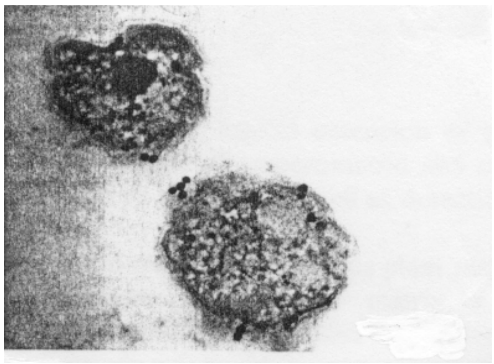


Selective apoptosis-inducing activity of hormone-anchored metal conjugates against MCF-7 breast cancer cells

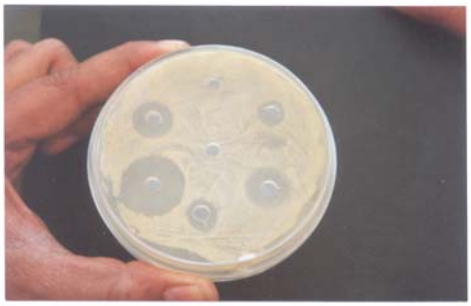
Other approach used in our lab is creating synthetic metal conjugates for generating H_2O_2 in cancer cells selectively which can trigger corresponding signal transduction processes leading to apoptosis. Multidonor ligands capable of organizing polynuclear metal clusters have been found to be especially effective compounds against estrogen independent BT 20 breast cancer cells and androgen dependant prostate cancer PC3 cell line.

2. Drug Design for Tuberculosis:

Tuberculosis remains the single leading cause of death worldwide due to an infectious disease. The disease has posed serious threat to global health due to its spread among the immuno-compromised individuals and rapid emergence of drug resistance to most of the first-line of antitubercular drugs. In our laboratory work is progressing on antitubercular drugs which can be transported into mycobacteria using siderophoric fragments for rapid internalization with appended pharmacophores for targeting intracellular enzymes or metal-chaperone proteins. The synthetic work is carried out using a combinatorial approach employing parallel synthesis. From a library of few hundred compounds, we have been able to identify some promising candidates whose activities are currently being optimized. Two novel targets explored in our laboratory include anti-salicylate compounds and ICL inhibitors.



Subcellular Cu-Zn SOD targets

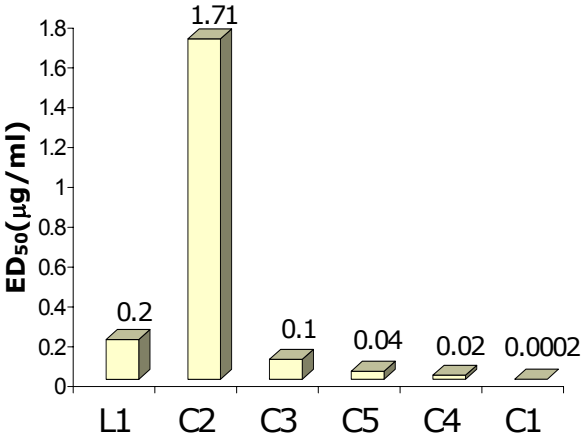


Antimycobacterial activity of new compounds using Disc Diffusion Assay

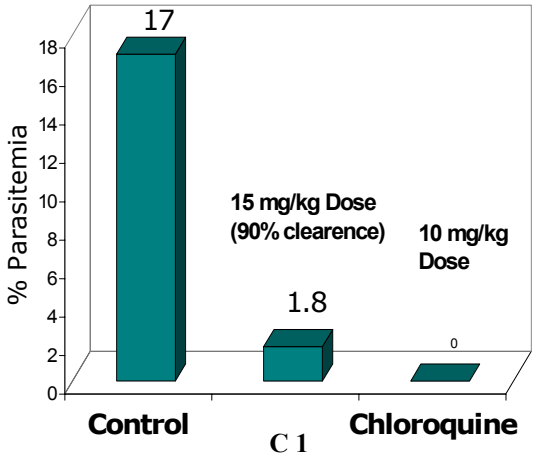
4. Drug Design for Leishmaniasis and Malaria:

Nearly half of the global population lives under the continuous threat of two tropical diseases viz. malaria and leishmaniasis. Approximately two million deaths per year take place due to malarial infections while nearly 15-20 million people are estimated to be infected with leishmaniasis world wide. The situation has become critical in recent years due to the acquired resistances for the available drugs and their side effects.

The drug design strategy followed in our group is based on the preferential nutritional need for the heme groups of the leishmanial and malarial parasites. In another approach modified structural analogs of mitochondrial respiratory intermediates are targeted using analogues whose activities are synergistically enhanced through metal conjugation.



In vitro antimalarial activity against *P. falciparum* 3D7 (chloroquine sensitive)



In vivo antimalarial activity against *P. berghei* (ANKA strain)

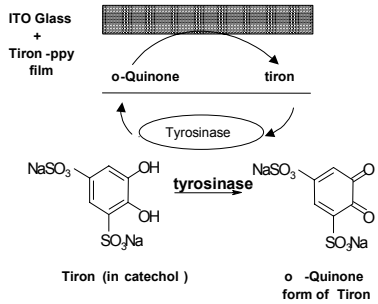
5. Conjugates of Non-Steroidal Antiinflammatory drugs as Cancer Reversal Agents:

A dramatic recent development in oncology is the recognition that some of the Non-Steroidal Antiinflammatory Drugs (NSAIDs) with potential of inhibiting key enzymes in inflammation can delay or prevent certain forms of cancers. The best understood example of NSAID therapy in oncology involves reversal of colon cancers where multiple lines of evidence in animal and cell culture experiments, therapeutic trials and epidemiological studies indicate that they are able to block colon carcinogenesis in early stages. The key to use NSAIDs in cancer reversal is the modification and appendages of these molecules by appropriate pharmacophores. In our laboratory some of these strategies are identified through *in vitro* and *in vivo* screenings. The lead molecules are now put through the toxicological screens and prepared for clinical trials.

6. Biosensors for Clinical Diagnostics :

Work on biosensors in our laboratory is a logical extension of our work on targeted drug design and deals with design and construction of amperometric and optical fibre sensors for the detection of biomarkers for various pathophysiological disorders in body fluids for diagnostic purposes. For example, in one of the projects, conducting polymers are used for immobilising modified catecholic reagents for

determination of monophenolase activity of fruit juices. This sensor is particularly suitable for monitoring quality of the commercial beverages.



Schematic diagram of the sensor using conducting polymer

A recent project deals with detection and monitoring real-time changes in cell behavior *in vitro* which is aimed at examining the effects of new potent anticancer agents on human malignant cells. The probe is based on the idea that early changes in the open circuit potential (OCP) signals relative to control treated cells, reflect modifications of physiological processes initiated by the anticancer drug molecules.

(Updated on December 1, 2003)