Theme 1

Virtual screening and High throughput screening for herbal drugs based on molecular Markers

High-throughput Identification of Bioactive Markers of Astavarga plants: *Roscoea purpurea*

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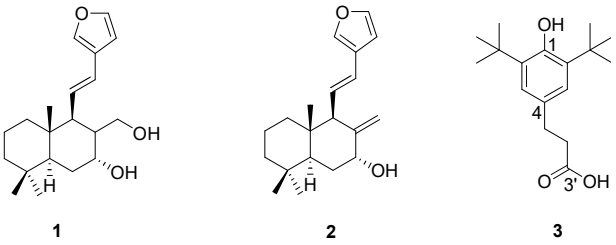
Abstract

In our ongoing research program to discover bioactive natural products from natural resource especially from high altitude with profound biological activities, our interest was focused on the *Roscoea purpurea* (rhizomes) commonly known as "kakoli". *Roscoea purpurea* is an essential ingredient of an important Ayurvedic preparation known as *Astavarga*, which is a group of eight medicinal plants claimed to be useful in promoting body fat, healing fractures, seminal weakness, fever, abnormal thirst, diabetic conditions and as a cure for vata, pitta, rakta doshas. *Astavarga* plants are considered as very good *Rasayana* with rejuvenating and health-promoting properties, and are known to strengthen the immune system and have immense cell regeneration capacity. *Astavarga* plants are also reported to restore health immediately and work as antioxidants in the body. Amongst eight Astavarga plants *Roscoea purpurea* is one of the essential ingredients of several herbal formulations like tonic and Chyawanprash. Traditionally it is used for the treatment of diabetic, hypertension, diarrhea, fever, inflammation etc. In Nepal, the tubers are boiled for edible purpose and also used in traditional veterinary medicine. We were mainly interested in the traditional use of the rhizomes of *Roscoea purpurea* as immuno-potentiating agent. In the view of its importance in traditional medicinal system, no substantial phytochemical and pharmacological works have been carried out. Previous phytochemical investigations on *R. purpurea* have described the isolation of two principal groups of compounds, steroids and phenolic derivatives. To date, only few compounds have been identified and quantified through HPLC analysis from tubers of this plant by Singh and co workers, and they are presumed to be associated with its potent antioxidant activity.

Ethanolic extract of the plant have shown *in-vitro* anti cancer and anti-oxidant activities. In this study, a fraction of the crude extract guided by the anti-cancer bioactivity led to the isolation of potent anticancer compounds **1-3** along with several known compounds. The structures of isolated compounds were elucidated by detailed spectroscopic 1D/2D analysis. In this presentation, we will talk about isolation, structure elucidation and anticancer activity of compounds **1-3** and established these compounds as a marker compound of this plant. We will also discuss different methods used to prove the authenticity of natural origin of **3,** a rare 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propanoic acid commonly known as Fenozan acid (FZA).



Keywords: Astavarga, Anticancer, antioxidant

Ethnopharmacology and biomarker development and drug discovery from herbal drugs

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Abstract

Over the years, research on ethnomedicine has originated new thoughts and applied their domain of knowledge to modern health sciences. In spite of the advanced medical technology and modern medicines, traditional knowledge and folk medicine system are still prevalent for therapy of different ailments. The prime concern of ethnomedicine is the existing relationship between disease and environment (human adaptation and socio-cultural behavior), that how peoples of different tribal groups look into the diseases and illness towards prevention and cure on the cultural and social organization perspective. In this context, documentation of traditional knowledge on health care practices and linking them to the biomarkers for individual diseases is very helpful in discovery of valuable drugs used in the modern society.

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Herbs and herbal products/formulations have been traditionally used for the management of Human heath from the ancient time. Ethnopharmacology is a multidisciplinary field of inquiry investigating the anthropological rationale and the pharmacological basis of the medicinal use of plants, animals, fungi, microorganisms, and minerals by human cultures. Ethnopharmacology plays a major role in the evaluation of natural products, and more distinctly herbal drugs from traditional and folklore resources. It has the aim of validating traditional preparations, either through the isolation of active substances, or through various pharmacological as well as therapeutic findings. The pharmacological properties, mechanisms of action, drug interactions, safety, and efficacy evaluation of herbal medicines are required for consumers and health care providers to maximize the therapeutic benefits and to avoid unwanted effects. Quality control of herbs/herbals is utmost essential to define the status of a drug in terms of purity, content, physical and biological properties. Chemoprofilling and marker development is required to ensure the quality related aspects of herbs/herbals. DNA based marker development together with disease based marker development of the natural products with the intervention of interdisciplinary, multidisciplinary and trans-disciplinary research for the development of scientifically validated products. This approach will contribute to develop of standardized, synergistic, safe and effective herbal products with robust scientific evidence towards the development of effective new generation therapeutics.

Keywords: Ethnomedicine, Herbs, Pharmacological properties.

Role of Biomarkers in Herbal Drug Targeting

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Abstract

Biomarkers or biological marker is widely used to measure what is happening in a cell or an organism at a given moment. Biomarkers can serve as early warning systems for our health. For example, high levels of lead in the bloodstream may indicate a need to test for nervous system and cognitive disorders, especially in children. High cholesterol levels are a common biomarker for heart disease risk. Utilization of biomarkers has a potential to make drug discovery, development and approval processes more efficient. Biomarkers of disease play an important role in drug discovery and development. Our country has a vast knowledge of Ayurveda and herbal medicine but administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. This novel approach can reduce the limitations of traditional drug delivery systems. With the magical concept "old drug in new cloths" biomarkers can be use for target of herbal medicines. It may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. Selection of careers in target drug delivery system is very important for successful drug targeting of drugs. Many researchers suggest that Exosomes have enormous potential as a drug delivery vehicle due to enhanced biocompatibility, excellent payload capability, and reduced immunogenicity compared to alternative polymeric-based carriers. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. As a conclusion, potential benefits, challenges and opportunities of using biomarkers in herbal drug are summarized and discussed.

Keywords: Biomarkers**,** Herbal medicines, herbs, targeted drug delivery system

Smart and Intelligent Techniques in Drug Designing

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Abstract

Smart and intelligent computational techniques in drug designing are essential nowadays for designing, manufacturing, and optimizing new drugs. New and innovative computational tools and algorithms are consistently developed and applied for the development of novel therapeutic compounds. Rapid developments in the architecture of computers have also provided complex calculations to be performed in a smart, intelligent, and timely manner for desired quality outputs. When we think of new technologies in medicine, we tend to conjure images of futuristic artificial intelligence (AI) computers, 3D-printed organs, and robot surgeons. The ambitious and lesser-explored methods currently being applied in drug discovery and development, however, could prove to be just as exciting. Various smart and intelligent techniques have been developed like structure & ligand-based drug design, quantum mechanics, molecular dynamics, target prediction, ADMET calculation, artificial intelligence & machine learning, gene writing, virtual trials etc. Nevertheless, it is likely that for smart and intelligent techniques to achieve success, even with the best

combination of innovative technology and predictive knowledge, there will always be a critical requirement for creativity, inspiration, perseverance and teamwork from the scientists involved.

Keywords: Computational technique, Drug designing, ADMET.

Exploring potential biomarkers for colorectal cancer metastasis, using high-throughput quantitative proteomics approach

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Abstract

Colorectal cancer (CRC) is the second most common cause of death among the cancer patients throughout the world. Although over the past decades, modern surgical techniques and improved radio-chemotherapeutic regimens have increased the overall survival rates, almost 50% of these patients eventually developed recurrent disease and metastasis leading to death within 5 years of diagnosis. Most of the attempts to diagnose or treat the CRC metastasis, have not been successful because they targeted only one or two proteins despite metastasis being caused by multiple factors. Hence at present, opting for a combination therapy targeting multiple proteins seems to be the most suitable alternative, which calls for detailed understanding of the global proteomic alteration occurring within the cells. Acquisition of such voluminous information at a high degree of confidence is not feasible by using the traditional reductionist approaches in molecular biology. Use of high throughput quantitative proteomics approach such as iTRAQ (isobaric tags for relative and absolute quantitation), provides the opportunity to study dynamic cellular alterations at a global proteome level. Using high-throughput quantitative proteomics (iTRAQ-based) along with advanced cell and molecular biology tools, we identified Calcyclin Binding Protein (CacyBP) as one of the potential candidate biomarkers for CRC metastasis. This was followed by a detailed mechanistic investigation of CacyBP mediated CRC progression that were derived to be enhanced cell motility via increased endocytosis and recycling of integrins to the leading edge of the cell and enhanced actin nucleation (Ghosh et al., 2013). iTRAQ-based proteomics was also utilized to explore the large repertoire of exosomal metastatic factors that can communicate with the tumor microenvironment as well as cells at distant site that helps in intercellular crosstalk between parent tumor and distant cells and thereby play crucial role in establishing distant metastasis. Our current research is focused on in-depth molecular analysis for understanding the metastasis in CRC, by studying vital cellular events such as single cell movement and epithelial mesenchymal transition, in the context of exosome mediated metastatic signal proteins.

Keywords: Colorectal cancer, Protein, Metastasis.

Advances in Natural Product Drug Discovery through Combined *in silico* Approaches

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Abstract

Natural products represent an important source of new lead compounds in drug discovery research. Several drugs currently used as therapeutic agents have been developed from natural sources; plant sources are specifically important. As computer technology has developed, *in silico* approaches such as molecular modelling, virtual high-throughput screening, natural product library, database mining and network analysis have been widely utilized in efforts to elucidate the pharmacological basis of the functions of traditional medicinal plants. In the process of new drug discovery, the application of virtual screening and network pharmacology can enrich active compounds among the candidates and adequately indicate the mechanism of action of medicinal plants, reducing the cost and increasing the efficiency of the whole procedure. The bioactive natural products can be used as lead compounds for the optimization of structural features to develop new and more effective analogues by applying modern medicinal chemistry approaches, including molecular modelling and combinatorial chemistry. In the modern drug discovery of natural products, the isolated new compounds possessing acceptable bioactivity are subjected to SAR studies and molecular modeling processes to design and develop analogues with more potency, fewer toxic effects, and better pharmacokinetic profiles. Study through *in silico* methods can also reveal that interaction with certain enzymes may influence the test compounds' biological activity. Recent research trends in natural product drug discovery clearly indicates that natural products will play important role in the future development of new therapeutic drugs and it is also anticipated that efficient application of new approaches will further improve the drug discovery campaign.

Keywords: Virtual screening, Network pharmacology, High-throughput screening, Drug discovery.

Cytotoxic activity, molecular docking, and pharmacokinetic properties of the Nyctanthin from

***Nyctanthis arbortristis* L.**

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Abstract

Natural products have gained a wide popularity as chemopreventive and anti-cancer agents owing to their multi-mechanistic mode of action, availability and synergism with several conventional chemotherapeutic agents. Nyctanthin is a carotenoid compound isolated from the hydroalcoholic extract of leaves and seeds of *Nyctanthes arbortristis* L. (Pariajt). Its structural characteristics were investigated by the UV, IR, ^{1}H NMR, C^{13} NMR, COSY and MASS spectroscopy. MTT assay were used to assess anti-cancer properties of Nyctanthin. It has shown promising effects as an anti-tumor agent in cell culture systems. Nyctanthin retards the growth of cancer cells *via* inhibiting nucleic acid synthesis, enhancing anti-oxidative system, and inducing apoptosis and differentiation pathways. Further studies involves molecular docking showed that Nyctanthin exhibits strong affinity for EGFR as evidenced by the negative docking score and binding free energy (BFE) values. Therefore, Nyctanthin from *Nyctanthes arbortristis* showed antiproliferative effect possibly by inhibiting EGFR.

Keywords: Nyctanthes arbortristis L., Parijat, Phytochemical, Cytotoxic, Molecular docking

QSAR study on benzimidazole derivatives: A comprehensive computational approach towards lead identification for colorectal cancer

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Abstract

Colorectal cancer (CRC) is a disease with high incidence and mortality, constituting the fourth most common cause of death from cancer worldwide. Benzimidazole derivatives are attractive compounds due to their structural and antiproliferative properties. In this work, such benzimidazole derivatives are chosen which are reported with their anticancer activity without computational analysis. QSAR studies being an important part of in-silico approach; plays a principal role in drug designing and molecular modeling. In this context, the 2D & 3D QSAR studies of the congeneric series have been performed using Schrodinger Maestro 13.1. Where 3D QSAR uses adjacent chemical environment data of a specific spatial arrangement of a moiety using a force field, on the other hand, 2D QSAR uses topical data of a molecule. According to the acceptability and reproducibility of QSAR analysis, 3D QSAR is vividly used to do molecular modeling. So, performing both studies, the contour map of atom-based 3D QSAR has been used to design novel benzimidazole derivatives, which can be further implemented in the upcoming research in the field of CRC treatment.

Keywords: Colorectal cancer, Benzimidazole derivatives, 2D and 3D QSAR, Contour Map, Atom based 3D QSAR.

Deorphanization of Orphan GPR52 Receptor by *in-silico* Modelling

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Abstract

Human body comprises of number of proteins which have the involvement in a large number of biological processes. Receptors are the proteins which govern the physiological functioning of human body. G-protein coupled receptors are belongs to the largest family of receptors which situated on the cell surface having seven trans- membrane proteins as their structural domain and have ability to activate intracellular transducer G-protein after binding with indigenous/exogenous ligands. Their ligands mainly the extracellular transmitters have a wide diversity of size, shape and chemical properties including protons, ions, biological amines, nucleotides, amino acids, peptides and lipids. GPCRs play key role in cell-to-cell communication and they regulate the wide variety of physiological and pathophysiological processes.

GPCRs membrane proteins are targeted by a variety of marketed drugs. They belongs to the largest family of more than 800 of known membrane proteins in which some proteins are considered as orphan receptor protein because either their endogenous ligands are not available or discovered yet. These orphan receptor proteins become the promising target for a large variety of diseases or disorders like cancer, psychiatric disorders, brain malformation, neurodegenerative disorder and hormonal disorders etc. GPR52 receptor co-situated in medium spiny neuron with dopamine receptor, expression of GPR52 in MSNs increase the cAMP level hence oppose the action of Dopamine D2 receptor, also facilitate the Dopamine D1/NMDA receptors. These receptors play vital role in many psychiatric disorders hence the GPR52 orphan receptor may become the newer target for the treatment of various

psychiatric disorders. We had prepared the dataset of 81 compounds from different research articles and performed the molecular docking and pharmacophore mapping studies. The results found from these studies were promising and satisfactory.

Keywords: GPCR, Orphan Receptor, Neurodegenerative Disorder, Docking, Pharmacophore mapping.

Synthesis and *in-silico* analysis of some novel Nitrogen-containing heterocyclic compounds

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Abstract

Cancer is a critical disease in the present century affecting the worldwide population. There are several chemotherapeutic medications for the treatment of cancer. However, they are associated with some drawbacks like cancer resistance, toxicities and adverse effects. Thus, the search for appropriate antitumor medication continues to be occurring. Heterocyclic compounds are considered one of the vital classes of organic compounds, which are used in many biological fields, due to their activity in multiple illnesses. Biological molecules such as DNA and RNA, chlorophyll, hemoglobin, vitamins and many more contains the heterocyclic ring in the major skeleton. More than 85-95% of new drugs contain heterocycles that have bright scientific insight into the biological system. It was found that the indole ring system has become a key structural element in modern medication and its derivatives demonstrate a various array of biological and pharmacological activities e.g., anticonvulsant, antibacterial, antifungal, antiviral, antimicrobial as well as potential anticancer properties. In the current work, we have performed *in-silico* analysis and synthesis of novel indole derivatives via the Michael Addition reaction between indole and substituted chalcones. These synthesized compounds were evaluated for anticancer activity with significant results.

Keywords: Synthesis, *in-silico* analysis, heterocyclic compounds, Michael Addition, Anticancer activity

Molecular distinction amongst varieties of Ashwagandha using RAPD markers

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Abstract

Ashwagandha (*Withania somnifera*) has been used extensively in Ayurveda and Unani systems of Medicine from more than 5000 years. In Ayurveda, it has been designated as "Sattvic Kapha Rasayana" that acts as a health promoter, rejuvenator and tonic. All the parts of Ashwagandha viz. seeds, leaves, fruits, roots have been used by used by Ayurvedic practitioners. It has plethora of pharmacological activities such as anti-cancer, anti-alzheimer, anti-parkinson, anti-schizophrenic, anti-stress, neuro-protective, anti-inflammatory, anti-diabetic, anti-microbial, anti-arthritic, adaptogenic, cardio protective, hepato-protective, immunomodulatory properties, anti-hypoxic, anti-ischemic, aphrodisiac, etc. Improved varieties of Ashwagandha have been developed for marketable production in various parts of the country. However, not much work has been carried out on the molecular characterization of these varieties. Random Amplified Polymorphic DNA (RAPD) is an important tool to analyze genetic diversity and identification of medicinal plants. Eight varieties collected from five different geographical locations were analyzed using seven arbitrary sequence RAPD primers. Six RAPD primers produced the same banding pattern in all the varieties and unique pattern was observed with 02 primers which could be used to discriminate the varieties of Ashwagandha used in the study based on DNA fingerprinting pattern. SCAR markers could be developed for one variety for its identification. Furthermore, cluster analysis using RAPD bands produced a phylogenetic tree of genetic relatedness that was in accordance with taxonomic classification. Thus the Ashwagandha varieties could be distinguished by their RAPD profiles.

Keywords: Ashwagandha, Molecular markers, RAPD, SCAR, *Withania somnifera*

Pharmacophore mapping-based virtual screening for the development of novel anti-cancer agent against hepatocellular carcinoma

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Abstract

One of the disorders with the greatest mortality rates is cancer and hepatocellular carcinoma the fifth most common cancer

and the second most frequent cause of cancer-related death globally the . There is no effective treatment for it, which is one of the factors contributing to its high mortality rate. Therefore, a key aim in the treatment of cancers is to discover medications that can successfully inhibit malignant tumours. The functional moiety of an analogous drug can be changed to either boost or decrease the potency of the drug. Pharmacophore modelling enables one to acquire an in-depth understanding of drug target efficacy and mapping to understand their interaction. To treat any condition, it is necessary to design the compounds by identifying the active functional pharmacophore. Understanding the interaction between the compounds and the target active site pharmacophore is made easier by mapping of commercially accessible database chemicals. In this present study virtual screening, via best, pharmacophore model has been utilized to identify novel anticancer agent against hepatocellular carcinoma. Pharmacophore model is generated by using series of naphthylamide derivative by the help of Schrodinger and zinc data base used for the virtual screening.

Keywords: Hepatocellular Carcinoma, pharmacophore mapping, virtual screening, naphthylamide.

Development and evaluation of homology model of human GPR119 protein as a potential drug target for NIDDM

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Abstract

Homology modelling is a protein sequence with unknown structure is aligned with sequences of known protein structures. Homology modeling predicts the 3D structure of a query protein through the sequence alignment of template proteins. The necessary condition for successful homology modelling is a sufficient similarity between the protein sequences. The importance and applicability of homology modelling is steadily increasing. Homology modeling has many applications in the drug discovery process. We generated homology model by predicting the structure of the G-protein coupled receptor 119, which involved in Diabetes Mellitus Type II. In this method, the 3D structure of a protein is obtained with the following steps: (i) identifying the proper template (ii) sequence alignment (iii) alignment corrections (iv) backbone generation (v) loop modeling, (vi) side chain modeling (vii) optimizing the model (viii) validating the model. This contributes to the identification of novel drug candidates. Homology modeling plays an important role in making drug discovery faster, easier, cheaper, and more practical.

Keywords: G-protein coupled receptor, Diabetes Mellitus Type II, protein structures.

Molecular docking of COX Inhibitors

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Abstract

Molecular docking is a key tool in structural molecular biology and computer assisted drug design. It can predict different binding modes of ligand in the groove of target molecule this can be used to develop more potent, selective and efficient lead optimization. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypothesis of how the ligands inhibit the target, which is invaluable in lead optimization. Docking studies were performed to explain the possible interactions between the inhibitors and both COX isoforms binding pockets. The major goal of the molecular docking analysis is to identify a molecule with a high affinity for the target protein COX-2 and to create a stable compound. As a result, score functions can be used to estimate the frequency of the interaction between the two molecules. The stability of the complex increases with ranking.

Keyword: Molecular Docking, COX Inhibitors, ligand-protein docking.

Computational studies of novel Isoxazole-Piperazine derivatives as potential anticancer agents for Hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma is the most common type of liver cancer accounting for about 75% of all primary liver cancers and is the 6th most frequent and the 2nd deadly cancer worldwide. Quantitative structure-activity relationship (QSAR) analysis has speeded up the lead optimization process by multiple degrees in the last two decades. QSAR methods are important for the prediction of

biological effects of chemical compounds based on mathematical and statistical relations. We have applied QSAR studies on novel series of isoxazole-piperazine derivatives that act on hepatocellular carcinoma by targeting different pathways which are efficiently useful for the treatment of Hepatocellular carcinoma.During QSAR studies we found some efficient derivatives of this novel series ofisoxazole-piperazine that induced G1 or G2/M phase arrests resulting in apoptotic cell death.

Keywords: Hepatocellular carcinoma, Quantitative structure-activity relationship (QSAR), cell death

Acute Toxicity Determination of Bioactive Flavonoid Apigenin in 4 Weeks Old Wistar Albino Rats

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Abstract

Aim: The aim of the study is to determine the acute toxicity of apigenin in vivo in 4-weeks-old Wistar albino rats. **Methodology:** Rats were orally administrated single dose of 100,500 and 1000 mg/kg apigenin and the control group received vehicle orally. There were 10 rats in each group. All animals were sacrificed after 14 day so treatment. Eight parameters were tested: cage side observation, body weight measurement, food and water consumption, blood pressure, absolute and relative organ weight, hematology, biochemical analysis, to look for evidence of toxicity. **Result**: No mortality was noted after14days of treatment. In general, behavior, food and water consumption, hematological studies and organ weights showed no significant changes. The apigenin increased rat blood systolic pressure after an hour of 100, 500 and 1000mg/kg doses, respectively. Biochemical studies showed significant elevation of ALT, AST, albumin, triglycerides, cholesterol and albumin ($p>0.05$), at all levels of doses. But, nephrotoxicity evidenced by elevated creatinine was seen only at a dose of 1000 mg/kg. **Conclusion**: Oral administration of apigenin resulted in increasing rat blood pressure after an hour of drug administration. The highest dose of apigenin also induced acute severe hepatotoxicity and mild nephrotoxicity. However, apigenin shows no effects on body weight, food and water consumption, absolute and relative organ weight and also hematology parameters.

Keywords: Acute Toxicity Determination, Bioactive Flavonoid, Apigenin, Wistar Albino Rats, Biochemical Studies