Medicinal Chemistry Conference

(MedChem – 2019)

on

Natural Product Prospecting for Therapeutic Applications

November 1-2, 2019

organized as part of the activity of IITM - AstraZeneca Endowment for Education and Research in Medicinal Chemistry

Department of Chemistry

Indian Institute of Technology Madras, Chennai

(http://chem.iitm.ac.in/medchem2019/)

Medicinal Chemistry Conference
(MedChem – 2019)

Abstracts

Indian Institute of Technology Madras, Chennai

November 01-02, 2019

Message from the conveners

On behalf of the organizing committee and the department of chemistry IIT Madras, it is our pleasure to warmly welcome you to MedChem-2019. This is the sixth (6th) Medicinal Chemistry Conference in the series. This event is part of our department's continuing efforts to promote Medicinal Chemistry education and research. This is being supported by an endowment from AstraZeneca Research foundation, India. Auspiciously, this event coincides with the diamond jubilee year of our Institute.

MedChem-2019 has a special focus on 'Natural Products Prospecting for Therapeutic Applications'. From many decades, natural products have been acting as a great source of therapeutic agents and have shown beneficial uses. Drug discovery using natural products is a challenging task for designing new leads in the process of discovering new and effective drug compounds. An event like this would be an ideal platform to know the past and present status of this area and to discuss about strategies to bring back the golden era.

In this one and half a day event, we are fortunate to have two special lectures and 12 invited lectures by eminent scientists actively working in the areas broadly represented by the title of the conference, like natural product isolation, total synthesis and medicinal chemistry, and also a panel discussion to enlighten the younger minds. There will be a poster session on the first day which will give a glimpse of research activities in these areas across the country. We are sure that the lectures, poster sessions and the panel discussion and this event will add two memorable days to our research life.

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Programme

MedChem 2019: Programme Schedule

Friday, November 1, 2019

08:00 – 09:00	Registration	
09:00 – 09:45	Inauguration	
	SESSION I	**Chairperson: Prof. K. Mangala Sunder**
09:45 – 10:30	Plenary Lecture	*Natural products and synthesis synergy: Med-Chem in the age of sustainability* **Prof. Goverdhan Mehta** National Research Professor, UoH, Hyderabad
10:30 – 10:45	**Tea break**	
	SESSION II	**Chairperson: Prof. S. Sankararaman**
10:45 – 11:30	Plenary Lecture	*Personal reflections of natural product chemistry in Big Pharma* **Dr. Robert J. Sheppard** AstraZeneca, Gothenburg, Sweden
11:30 – 12:00	Invited Lecture	*Hymn of herbs: Searching for panaceas from Western Ghats* **Dr. K. V. Radhakrishnan** CSIR-NIIST, Thiruvananthapuram
12:00 – 12:30	Invited Lecture	*Efforts towards Lead Identification through Natural Products Synthesis* **Dr. D. Srinivasa Reddy** CSIR-NCL, Pune
12:30 – 13:00	Invited Lecture	*New Bio-active Molecules from Indian flora (terrestrial, marine and lichens) and their therapeutic applications* **Dr. K. Suresh Babu** CSIR-IICT, Hyderabad
13:00 – 14:00	**Lunch**	
	SESSION III	**Chairperson: Prof. D. Karunagaran**
14:00 – 14:30	Invited Lecture	*Pancreatic beta cells regeneration by standardized Aloe vera extract: componentization and pathway studies* **Prof. M. A. Vijayalakshmi** VIT, Vellore
14:30 – 15:00	Invited Lecture	*Reversal of Polarity by SET Oxidation: Domino Synthesis of Heterocyclic Ring Systems* **Prof. S. Baskaran** Department of Chemistry, IIT Madras
15:00 – 16:15	**Tea break and Poster Presentation**	

	SESSION IV	
16:15 – 17:15	Panel Discussion	
17:15 – 17:45	Concluding Remarks for the Day	
19:30 – 22:30	**Banquet Dinner (by Invitation)**	

Saturday, November 2, 2019

	SESSION I	**Chairperson: Prof. Indrapal Singh**
08:45 – 09:15	Invited Lecture	*Prospecting Natural Products for Drugs* **Dr. K. Nagarajan** M/s Hikal, Mumbai
09:15 – 09:45	Invited Lecture	*Total Synthesis of Architecturally Intriguing Complex Alkaloids of Biological Relevance* **Dr. Alakesh Bisai** Department of Chemistry, IISER Kolkata
09:45 – 10:15	Invited Lecture	*Bioactive Molecules of Natural Origin* **Prof. Inder Pal Singh** CSIR-NIPER Mohali
10:15 – 10:30	**Tea break**	
	SESSION II	**Chairperson: Prof. G. Sekar**
10:30 – 11:00	Invited Lecture	*Natural products as "Bioenhancers"* **Dr. S. Arvind** SASTRA University, Tanjavur
11:00 – 11:30	Invited Lecture	*Biomimetic Total Syntheses of Biologically Active Natural Products* **Dr. Dattatraya H. Dethe** Department of Chemistry, IIT Kanpur
11:30 – 12:00	Invited Lecture	*Translational Research in Natural Product Drug Discovery and Development* **Prof. Sanjay M. Jachak** CSIR-NIPER Mohali
12:00 – 12:30	Invited Lecture	*Plant cell & Microbial Bio-factories for Sustainable Production of Phyto-pharmaceuticals* **Dr. Smita Srivastava** Department of Biotechnology, IIT Madras
12:30 – 13:00	Concluding Remarks and Valedictory Function	
13:00	**Lunch**	

END of the Conference

Plenary Lectures

Natural products and synthesis synergy: Med-Chem in the age of sustainability

Prof. Goverdhan Mehta

National Research Professor

University of Hyderabad, Hyderabad 500046, India

It is generally believed that natural products, med-chem and drug discovery, important components to achieve the ambitious mission of 'affordable health for all', are passing through considerable stress and need fresh and disruptive ideation. Chemistry has a pivotal role in this arena that range from adoption of sustainable technologies to enable green/circular manufacturing of APIs on one hand to accelerated NCE discovery from lead identification to clinic on the other, particularly for MDR and emerging diseases. With increasing concerns about environment and urgent need to minimize eco-foot-print and exercise resource prudence, new conceptualizations and approaches need to be devised to harness the full potential of the triumvirate of natural products, synthesis (chemical processes) and drug discovery. An effort will be made to capture the context and share some thoughts.

Personal reflections of natural product chemistry in Big Pharma

Dr. Robert J. Sheppard

Medicinal Chemistry, Research and Early Development,

Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

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Prospecting for therapeutic natural products is a powerful tool in the armoury of the drug hunter. Indeed, many approved drugs are natural products or their derivatives.[1] However, despite this rich history, many pharmaceutical companies have moved away from screening natural product collections in favour of high throughput screening of synthetic compound libraries.

In this presentation I will discuss some of the challenges associated with the identification and isolation of therapeutic natural products and highlight methods to overcome them.[2,3] Drawing on experience of the medicinal chemistry of natural products with antimicrobial and anti-cancer activities (Figure 1), I aim to show that natural products and their derivatives continue to have an exciting future in treating disease.

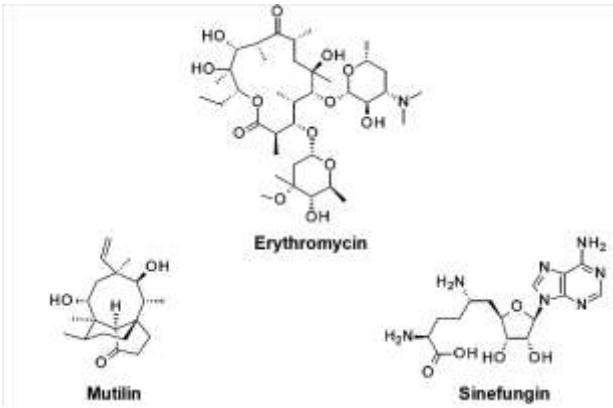

Figure 1. Examples of natural products with antibacterial activity or confirmed binding to a validated anti-cancer target.

References

1) Natural Products as Sources of new Drugs from 1981-2014; J. Nat. Prod., 2016, 79, 629-661.
2) Minimizing the risk of deducing wrong natural product structures from NMR data; Magn. Reson. Chem., 2019, 1-34.
3) Affinity Crystallography: A New Approach to Extracting High-Affinity Enzyme Inhibitors from Natural Extracts; J. Nat. Prod., 2016, 79, 9, 1962-1970.

Invited Lectures (IL)

Hymn of herbs: Searching for panaceas from Western Ghats

Dr. K. V. Radhakrishnan
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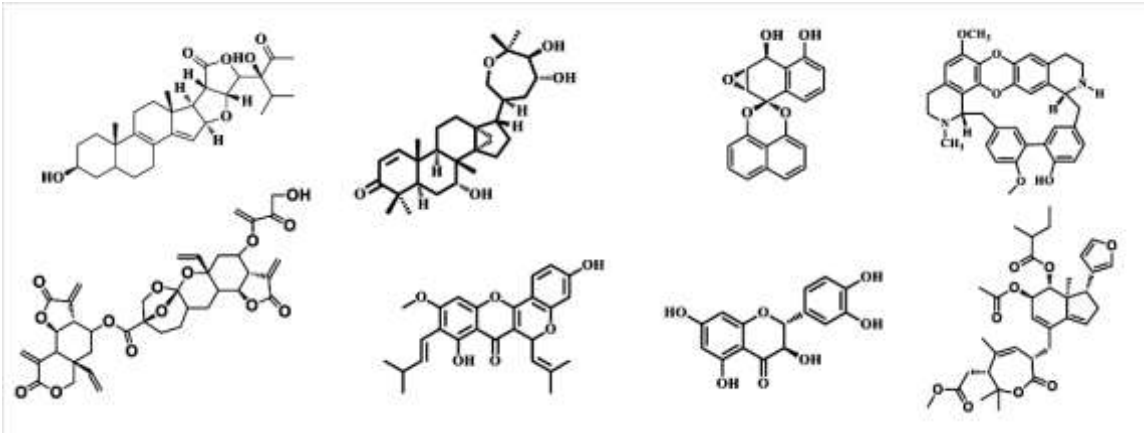
Information and knowledge on the chemistry, the availability pattern of the biochemical compounds vis-à-vis the ecology of such plant species and the nutrition value of most of the Kerala's food and health biodiversity is woefully inadequate today. Many of the traditionally cultivated or conserved species that have historically contributed to food, nutrition and health needs of the people (often those belonging to the poor and vulnerable sections) became neglected! It is imperative therefore for botanists, social scientists, agricultural scientists; natural product chemists, medicinal chemists, nutrition experts and biochemists to work together with the local community to produce evidence based knowledge that will help to take better decisions for the sustainable management of this dying biodiversity of India.

Along this line, we undertook the phytochemical and bio-evaluation of a selected group of high priority plants of Kerala for food, nutrition and health, with special emphasis on plants with proven activity based on traditional knowledge (Ayurveda, traditional healing practices, folk claims and oral health traditions of Kerala).



Some of the natural products under investigation

The results of our studies in this direction aimed drug leads for various ailments such as diabetes mellitus, CNS disorders, cancer with special emphasis on infections due to MDR strains of bacteria will be discussed.

New Bio-active Molecules from Indian flora (terrestrial, marine and lichens) and their therapeutic applications

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Principal Scientist
Centre for Natural Products and Traditional Knowledge,
CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, INDIA
Email: suresh@iict.res.in

Concurrent with human civilization, plants have been their true companions as source of medicine. These plants have contributed significantly in discovery, design and development of several modern medicines. Recent move of society towards nature for the treatment of various diseases where there is no satisfactory cure in modern medicine has diverted the attention of natural/medicinal chemists and biologists to unravel their chemical characteristics and biological activities together in order to define their therapeutic potential in the light of modern pathobiological understandings. This move has led collectively to rediscover, design and refine the therapeutic application of medicinal plants.

During last ten years, we have studied several medicinal plants/marine flora guided by *in vitro* based bioassays to delineate the chemistry of medicinal plants responsible for biological activities. This effort has led to identify several potent multiple active medicinal plants, their active fractions and synergistic molecular compositions. We have identified particularly, several free radical scavengers, cytotoxic and α-glucosidase inhibitory principles present in substantial yields in Indian flora. Presence of multiple active phytochemicals in rich concentrations in some of the medicinal plants therefore offers exciting opportunity for development of novel therapeutics and also provides scientific justification for their use in traditional medicines. The lecture covers isolation and biological activities of various new molecules isolated from natural sources *viz* medicinal plants and marine flora/fauna.

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Efforts towards Lead Identification through Natural Products Synthesis

Dr. D. Srinivasa Reddy
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Our research group at CSIR-NCL focuses on total synthesis of biologically active compounds and medicinal chemistry with an ultimate aim of discovering drugs. We have accomplished the synthesis of more than 30 natural products and prepared libraries of compounds around their scaffolds towards lead identification. They include cell-adhesion inhibitors, anti-bacterial, anti-malarial, anti-inflammatory and anti-cancer agents. In particular, I am going to discuss more details on three case studies (1) Solomonamides (anti-inflammatory) (2) Cladosporins (antimalarial) and (3) Hunanamycins (antibacterial). I will discuss about planning in choosing the target molecules, synthetic strategies to access sufficient quantities of the material and library synthesis, SAR with the help of appropriate biological studies and other efforts in identification of lead molecules for drug discovery programs in respective diseases.

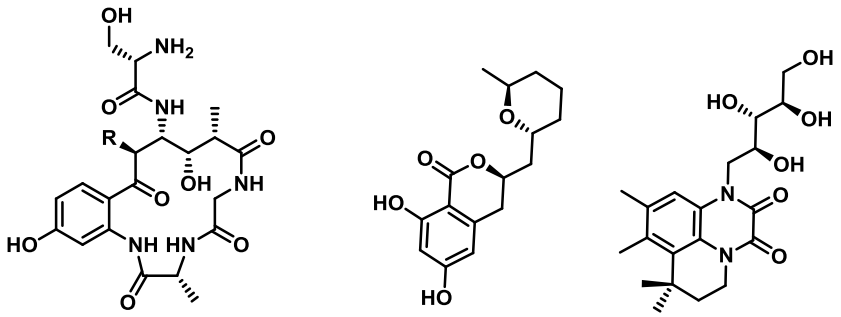

Figure. Structures of selected target natural products and their potential uses.

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Pancreatic beta cells regeneration by standardized *Aloe vera* extract: componentization and pathway studies

Prof. M. A. Vijayalakshmi
CBST, Founder Director, VIT University, Vellore – 632 014.

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and hypo-insulinemia. It has become a major health burden in our country. Chronic diabetes (type II) results either in the dysfunction or in the loss of insulin-producing pancreatic islet (beta cells). Previous studies carried out in our laboratory have shown that oral feeding of standardized *Aloe vera* extract for 3 weeks, alleviated diabetes in streptozotocin-induced diabetic rats showing the normal restoration of FPG and insulin levels (Noor et al, 2008). Parallely pancreatic beta cell regeneration was observed in these rats. Morphometric studies have shown the qualitative and quantitative rejuvenation of pancreatic beta cells (Noor et al, 2017). Organ-specific benefits were also observed wherein the inflammation in the liver was reduced and the excessive proliferation on the epithelium of small intestine was also reduced on feeding the diabetic rats with *Aloe vera* extract. We focused our efforts in understanding the mechanism of pancreatic islets regeneration and we hypothesized that the *Aloe vera* extract or its components may rejuvenate pancreatic islets either through inhibition of DiPeptidyl Peptidase (DPP)IV enzyme or through stimulaltion of Glucagon Like Peptide (GLP)-1 stimulated signaling.

To gain insights into the mechanism of action of rejuvenation of islets of the pancreas, group-wise fractionation of *Aloe vera* extract was carried out. The *Aloe vera* extract consists of three major groups of compounds *viz*. a) polyphenol anti-oxidants, b) peptide and protein and c) oligo/polysaccharides. In our approach to throw some light on the mechanism; we have fractionated the total extract into the above mentioned groups and studied them for the regenartion of the beta cells as well as two above mentioned biochemical pathways. It was observed that the polyphenol-rich fraction of *Aloe vera* extract has significant DPP-IV inhibition activity and the molecule has been identified through activity-based separation. The peptide/polypeptide fractions have rejuvenated the pancreatic islets and reduced the excessive proliferation of epithelium in the small intestine. These peptide/polypeptide fractions, through activity-based separation, have shown significant DPP-IV inhibition activity and hypothesized to be cyclic dipeptides. The oligo/polysaccharides have restored the pancreatic islets and reduced the inflammation and increased the glycogen content in the liver. The implications of these fractions from *Aloe vera* extract in the rejuvenation of pancreatic islets and hepatic functions will be discussed.

Reversal of Polarity by SET Oxidation: Domino Synthesis of Heterocyclic Ring Systems

Prof. Sundarababu Baskaran
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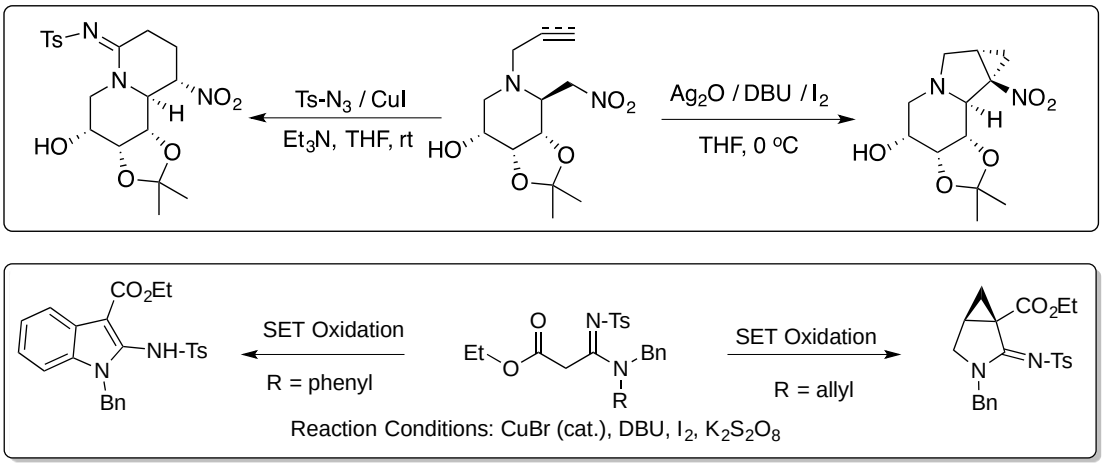
Heterocyclic ring systems bearing cyclopropane are ubiquitous in many biologically active natural products and in particular 3-azabicyclo[n.1.0]alkane framework is very common in many pharmaceutically important lead molecules.[1] As a result of their medicinal applications, several multistep synthetic approaches have been reported for the construction of 3-azabicyclo[n.1.0]alkane derivatives. The molecular complexity can be expeditiously created by combining two or more distinct reactions into a single transformation. In this context, single electron transfer (SET) oxidation of carbanion with reversal of polarity is one of the best ways of generating carbon-centered radicals, however the synthetic potential of the oxidative cyclization of carbanion strategy has not been fully explored in the synthesis of biologically important molecules. In this presentation, SET oxidative cyclization based cascade-strategies towards the stereoselective synthesis of biologically important molecules will be discussed.[2]



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Prospecting Natural Products for Drugs

Prof. K. Nagarajan
M/s. Hikal, Bangalore – 560 078.

The awards of Nobel prizes for physiology/medicine in 2015 for the discoverers of artemisinin and ivermectin validate the continued prospecting of natural products (NPs) for drugs. NPs are an important sources for drugs and drug leads. They possess enormous structural diversity unsurpassed by synthetic libraries. NPs occupy all the space of combinatorial libraries as well as additional volumes. New drugs from NPs stimulate advances in chemistry as well as biochemistry and medicine. There are multiple sources for NPs - plants, marine organisms, soil fungi and microbes etc. NPs do present problems as sources of drugs, often due their scarcity and difficulty of synthesis, inspiring efforts to make simpler derivatives, related closely or remotely. The concepts will be illustrated with examples. Fermentation offers unlimited access to NPs unlike plants. Approaches are available to get non NCE drugs from NPs by routes other than development of NCEs. The presentation will touch upon the Indian scenario.

Total Synthesis of Architecturally Intriguing Complex Alkaloids of Biological Relevance

Dr. Alakesh Bisai
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Nature produces a plenty of complex natural products and majority of these are isolated in entioenriched form (e.g. alkaloids **1-5**).[1] Since these are isolated from Nature in limited quantity (mostly in mg scale), total synthesis endeavours can play a crucial role in bioactivity evaluation by providing access to significant quantity. It also provides platform for the innovation of new strategies for chemical synthesis. Further, catalytic asymmetric construction of organic molecules sharing all-carbon quaternary stereocenter (see, **3-5**) is one of the challenging aspects of synthetic organic chemistry.[2] Enantioselective syntheses of targets having contiguous all-carbon quaternary stereocenters (see, **4a-b** and **5**) invariably face even more difficulty.

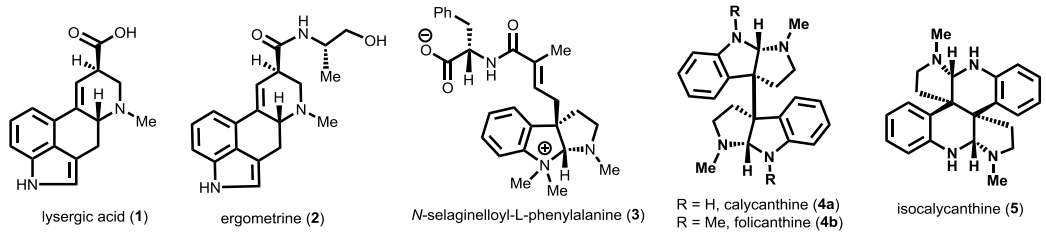

Figure. Architecturally intriguing indole alkaloids of biological relevance.

Towards this direction, naturally occurring tryptamine-based alkaloids (Figure) with impressive diversity of biological activities drew our interest for efficient total syntheses.[1a] Biosynthetically, they are imagined to be arisen from L-tryptophan. Interestingly, a variety of alkaloids of this family show antibacterial and cytotoxic activities.[1b] In order to devise strategy of above targets,[3] we explored novel methodologies that addresses core structure of these interesting alkaloids under mild condition.[4] Our synthetic endeavors towards the total syntheses[5] of architecturally intriguing indole alkaloids will be discussed.[6]

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Bioactive Molecules of Natural Origin

Prof. Inder Pal Singh
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Natural Products (NPs) have been used since ancient times for the treatment of many diseases. In the modern drug discovery programs, NPs from plants and microbes have been a traditional source of drug molecules. NP and traditional medicine (TM) based drug discovery strategies have re-emerged in the last few years or so after a decline in interest in NPs. In our continuous efforts for the discovery of new bioactive compounds, we have undertaken systemic investigation of isolation, characterization and bioactivity evaluation from medicinal plants and microorganisms. We have isolated several known and new compounds belonging to diverse chemical classes including terpenoids, flavonoids, alkaloids, pholoroglucinols, phenyl propanoids, phenyl glycosides, glycosides. The isolation, characterization and biological evaluation of some selected compounds will be presented.

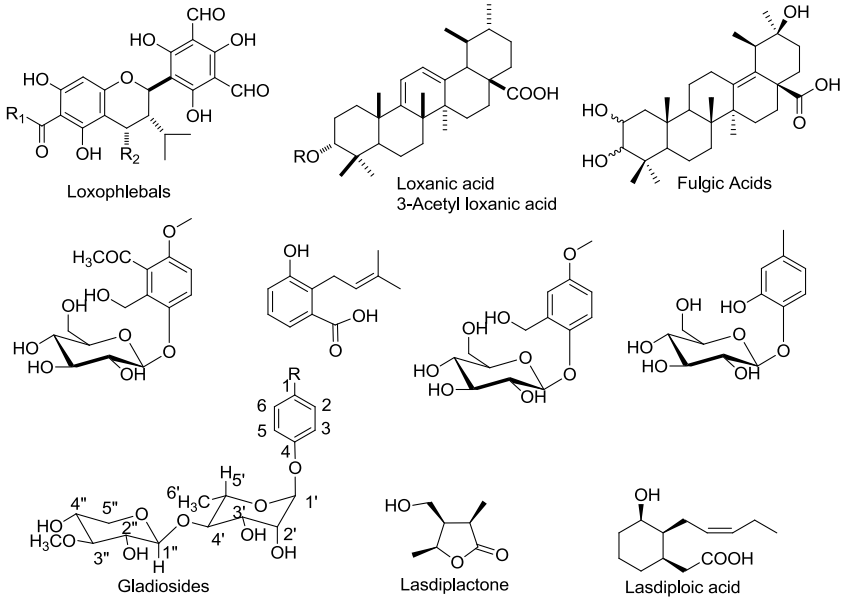

Figure 1. Structures of some new natural products isolated from plants and microorganisms.

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Natural products as "Bioenhancers"

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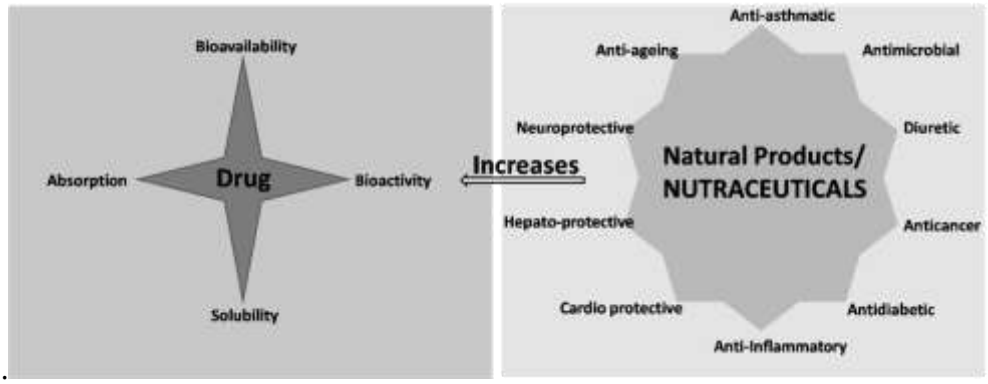
Bioavailability is "the rate and extent to which a therapeutically active substance enters systemic circulation and becomes available at the required site of action" [1] and and in addition, the excess drug/antibiotics administered, pose as a burden to the body, and may trigger the and "drug resistance".

A 'bioenhancer' is "an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used" [2]. Natural products and secondary metabolites, offer an amicable and viable proposition as 'bioenhancers' and can help in alleviating the side effects of therapeutic drugs and increase the life expectancy.



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Biomimetic Total Syntheses of Biologically Active Natural Products

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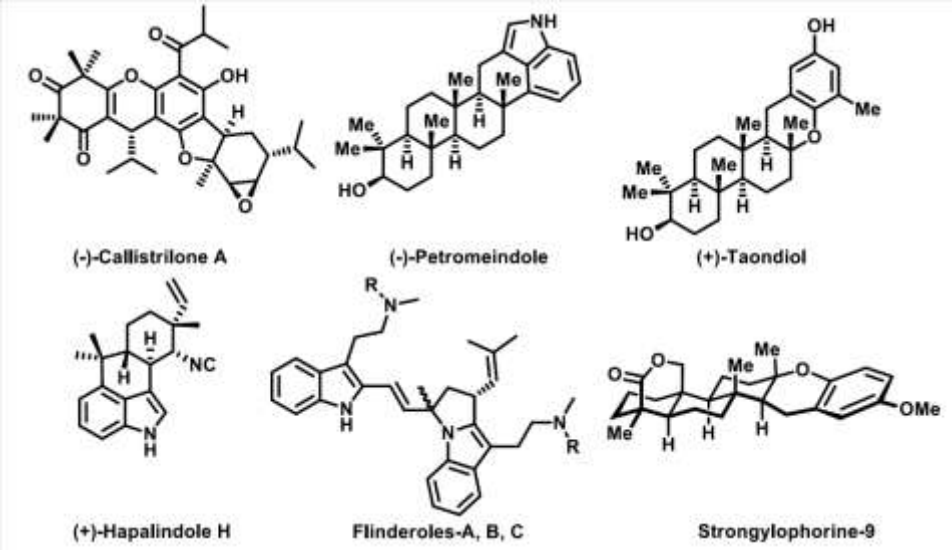
Abstract: The ever-growing field of total synthesis of natural products continues to be the source of inspiration for many synthetic chemists worldwide. Natural product synthesis also plays an important role in developing many areas of modern day biology. Synthesis of complex natural products for biological studies, using a minimum number of synthetic transformations, labor and material expenses presents significant challenges to organic chemists. Total synthesis in the 21st century should be an ideal synthesis, biomimetic pathways for total syntheses of natural products is considered as an ideal synthesis. Towards this goal we have achieved biomimetic total syntheses of callistrilones, petromeindole, hongoquercins, mycoleptodiscin A, murrayamines, flinderoles, strongylophorines, taondiol and hapalindole-H. Key steps features highly regio- and diastereoselective Friedel-Crafts alkylation between allylic alcohols and electron rich arenes/indole, [3+2] type cycloaddition, Michael reaction, Robinson-type annulation, Wacker type cyclization, double SN2′ cascade, diastereoselective epoxide opening, reductive Heck reaction, late stage oxidations, C-H activation and so on.



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Translational Research in Natural Product Drug Discovery and Development

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Natural products (NP) have been the most productive source of leads for the discovery and development of drugs over the years. Medicinal plants serves as one of important sources of drugs worldwide since they possess interesting biological properties. About 80% of the world's population uses plant/botanical-derived medicines which are called as herbal medicines. A considerable growth has been seen in the herbal medicine market in recent years as an alternative to medicinal products with chemically derived APIs. In drug discovery and development based on natural products of plant origin, there is requirement of potential plant resources as a source of lead molecules. In this aspect, exploring medicinal plant biodiversity provides rational approach to search for new medicines. At the same time in several traditional medicines throughout the world, medicinal plants constitute an important ingredient of medicines. India with its rich medicinal plant biodiversity in terms of three hotspots viz. Eastern Himalaya, Western Himalaya and Western Ghats, provide an excellent opportunity for drug discovery and bioprospecting. Given the fact that there are around 15,000 higher plant species occur in India out of which around 8,000 species are of medicinal importance; there is a great promise to explore Indian medicinal plants for evaluation of various biological activities.

There are several difficulties and challenges associated with the development of herbal drug products. The challenges mainly are related to regulatory guidelines, lack of knowledge of herbal medicines with the drug regulatory authorities, assessment of safety and efficacy, quality control, safety monitoring; for herbal drugs. All these challenges could be addressed effectively by promoting use of herbal drugs through application of modern scientific methodology to herbal drugs/natural products promoting translational research so that the value-added products can be developed. In this presentation translational approaches for product development from herbal extracts/bioactives will be enumerated with case study from ongoing research in our laboratory.

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Plant cell & Microbial Bio-factories for Sustainable Production of Phyto-pharmaceuticals

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It is estimated that herbal products (medicines) may reach market potential of 5 trillion dollars worldwide by 2050. Many in-demand high-value phytochemicals are chemically-complex secondary metabolites produced in plants. Increasing market demand has led to destructive harvesting and depleting natural resource, increasing the risk of such plants getting endangered or extinct, thereby leading to adulteration in the plant material during collection from the wild. Moreover, apart from the variation observed in different tissues of the same plant, the climatic and geographical variation in the yields of secondary metabolites in plants is well-known, leading to inconsistent and non-uniform product supply. Thus, there is a need for an environment-friendly, low-cost and sustainable alternative method of production, independent of nature. Hence, my research group's interest is in developing high-yielding plant cell and microbial biofactories which can be cultivated in large bioreactors for mass production of high-value, chemically-complex, low-volume plant derived bioactive compounds. In addition, the microbial and *in vitro* plant systems are amenable to genetic manipulation, process optimization and scale-up, unlike the natural plants, for selective increase in the yield and productivity of the desired-product at large scale with reduced downstream processing cost. Moreover, due to *in vitro* conditions, there is a possibility of expression in the cryptic gene clusters in these production platforms, leading to the discovery of novel bioactives, undetected in the natural plant. However, some of the challenges include qualitative and quantitative estimation of low-volume secondary metabolites in crude biomass extracts and low product yield in the *in vitro* systems than in the natural plants. Thus, an integrated and rational approach involving systems biology, bioprocess and metabolic engineering, chemical characterization and bioactivity analysis can be a more rational way forward to develop sustainable and high product yielding microbial and plant cell fermentation processes for commercial production of phyto-pharmaceuticals. To this effect, we have developed high-yielding transgenic sunflower cell lines[1] based on model predicted metabolic engineering strategy using a genome scale metabolic model, for enhanced production of the high-value anti-oxidant alpha-tocopherol. In another study, we used fourier transform mass spectrometry to identify and characterize known and novel cyclic peptides called cyclotides[2,3], for the first time in an Indian medicinal plant variety. Currently, we are working on developing high yielding plant and microbial based platforms[4,5] for the production of campothecin, the lead molecule for the anti-cancer marketed drugs, Irenotecan and Topotecan.

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Poster Abstracts

Identification of Phytochemicals as JAK2 Inhibitors

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Janus kinase (JAK) involved in JAK-STAT pathway plays a crucial role in cellular signaling. Mutations in JAK2 results in myeloproliferative and autoimmune disorders.[1] Thus JAK2 has become a potential drug target for the treatment of various cancers. 25 known JAK2 inhibitors were divided into training and test set and a 2D QSAR model was formulated with a correlation coefficient R^2=0.6584 for training set. The model generated showed good predictive power with Q^2= 0.6669. Based on this model phytochemicals were screened from Dr. Dukes phytochemical and ethnobotanical database.[2] Molecular docking studies were performed to explain the affinity of screened molecules to the target JAK2 protein. Arzanol was found to be the potent phytochemical with significant JAK2 inhibitory activity (figure 1). Hence its structural scaffold can be used as building blocks in designing new drug like molecules for JAK2 inhibition. QSAR studies and molecular docking studies of various chemicals having JAK2 inhibitory properties will be discussed during this presentation.

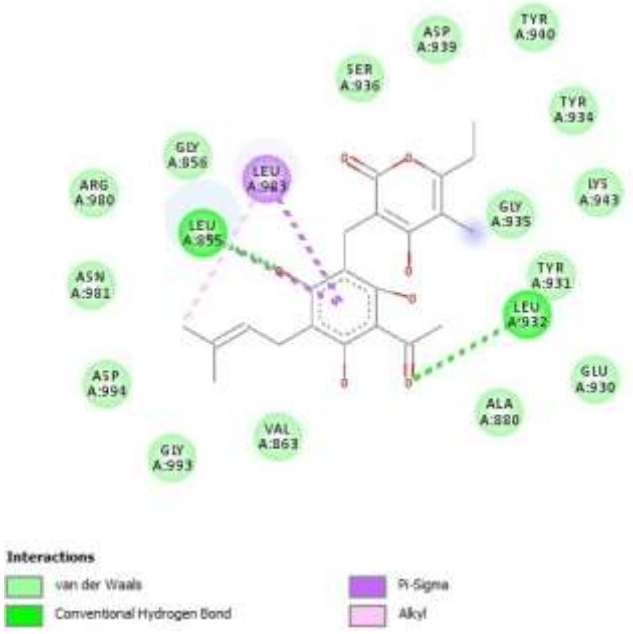

Figure 1. 2D interaction diagram of arzanol docked with JAK2 protein.

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P-2

Studies on Azelaic acid analogues as Histone Deacetylase (HDAC) inhibitors

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Histone deacetylase inhibitors (HDAC) are class of drugs which regulate epigenetic or non-epigenetic process, induces death, apoptosis and cell cycle arrest in cancer cells. Till now, FDA has approved four HDACs inhibitors i.e. Vorinostat, Belinostat, Romidepsin and Panobinostat. A small molecule of HDAC inhibitors identified so far fall into 3 distinct structural moieties: - the zinc binding group (ZBG), a hydrophobic linker and a recognition cap group. Our studies involving hydroxamic acid based- HDAC inhibitors were characterized by an Azelaic acid linker, capped with a substituted aromatic group. Total eight compounds ($AZ1_{a-e}$, AZ2 & AZ3) were synthesized. Computational studies of newly designed hydroxamate molecule (AZ3) showed better docking scores of -10.02 (PDB-IT69) as compared to Vorinostat (SAHA) (Fig1). Further systematic studies revealed that the synthesized hydroxamate molecules AZ3 showed good cell growth inhibitory activity with mean GI_{50} value of 23.1µM when screened against Prostate cancer cell line PC-3. Antibacterial and antifungal activities were performed where compound AZ1c was found to be active against *Salmonella typhi* at concentration of 3.125µg/ml and compound AZ2 was found to be active against *Aspergillus oryzae* at concentration of 3.125µg/ml.

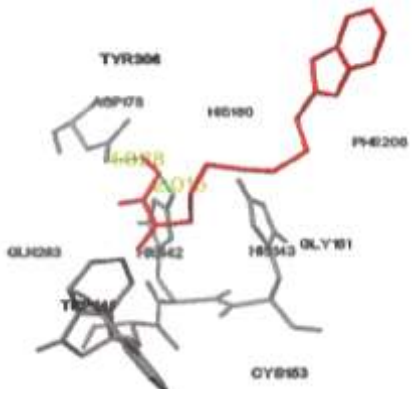

Figure 1: Three dimensional docking pose view of compound AZ3 with 1T69 receptor

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Synthesis of Photoswitchable Imidazolium Salts

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Altering organic transformations via external stimuli, such as light to tune intrinsic properties of a catalyst is of huge interest among scientists, especially those who are working in the field of artificial switchable catalysis.[1-3] A novel family of photoswitchable imidazolium salts, *N*,*N*′-bis(azobenzene) imidazolium chlorides are successfully synthesized by us. Towards this, azocoupling reactions of 4-substituted aryldiazonium chlorides with 2,6-dimethylaniline were performed under acidic conditions to yield 4-(aryldiazenyl)-2,6 dimethylaniline. Reactions of *azobenzene amines* with an aqueous glyoxal solution under conventional procedures to form diimines were found sluggish. To this end, successful conversion of the said amines to the corresponding diimines was achieved under modified reaction conditions. Treatment of the diimines with formaldehyde yielded our desired products *N*-heterocyclic carbene (NHC) salts (Fig. 1). Photoswitchable property of the azobenzene units attached to the imidazolium salts were studied via UV-visible spectroscopy and ^{1}H-NMR spectroscopy.[4]

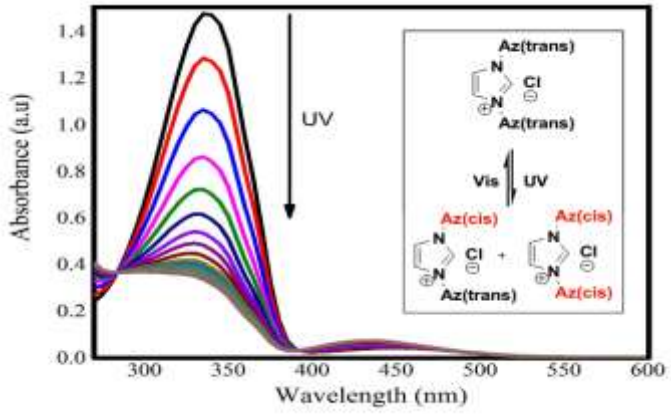

Figure 1. UV-visible spectra of imidazolium salt in dimethyl sulfoxide upon sequential irradiation with 365 nm UV light.

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Synthesis, Characterizations and Antibacterial Activity of Cyclodextrin-Benzimidazolium Ionic Liquids Based Inclusion Complexes

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Three inclusion complexes (ICs) have been synthesized by the combinations benzimidazole based ionic liquids (ILs) and β-cyclodextrin (β-CD) [1]. Formation of the ICs has been proved by the ITC. Further, ICs were characterized by ^{1}H NMR, 2D ROESY NMR, FTIR, TGA, DSC, HRMS and DLS. Additionally, morphology of the three ICs has been studied by SEM and TEM. Taking into account the fact that benzimidazole based derivatives have been utilized as potential anticancer agents [2], development of controlled release of benzimidazole containing ionic liquids from inclusion complexes is a desirable achievement. Efficacy of the ICs was established, as the bacterial growths were hindered through inhibition zone technique. Hence the present report displays the potentially of inclusion complexes of important biological molecules for developing a sustainable drug delivery applications.

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Design and Synthesis of Biological Active Polycyclic Systems from 2-Butyn-ols Through TfOH Self-relay Catalysis

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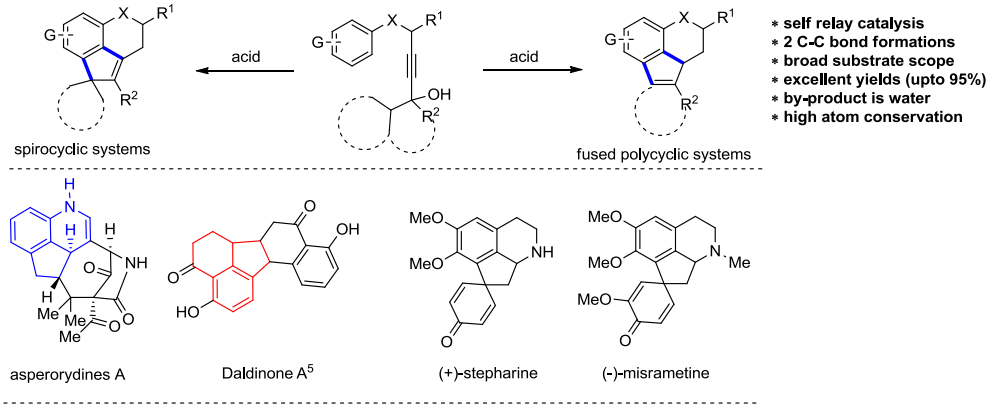
Ene-yne cyclization reactions are indisputably attractive atom-economical transformations in synthetic chemistry.[1] Fused tricyclic derivatives are important structural motifs found in a wide range of natural products and pharmaceuticals such as salviaprione,[3] ileabethoxazole,[2] neomangicol C[1] asperorydnes A, and (-)-Misramine constitute a very unique fused tricyclic core part and shows important biological properties against bacillary dysentery, diarrhea, abdominal pain, influenza, and antibacterial properties.[2] Only a few methods are reported for the synthesis of polycyclic compounds. We have developed a mild strategy for the synthesis of fused tricyclic compounds *via* dehydration of propargylic alcohol, hydro-arylation and Nazarov cyclization in turn to generate polycyclic system in a cascade manner, under acidic condition. The detailed reaction discovery and application will be discussed in the poster.



Scheme 1: Designed approach for the synthesis of fused polycyclic systems from propargylic alcohols and representative natural products

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P-6

Green synthesis, antitubercular evaluation and molecular docking studies of ethyl 3,5-dicyano-6-oxo-2,4-diarylpiperidine-3-carboxylate derivatives

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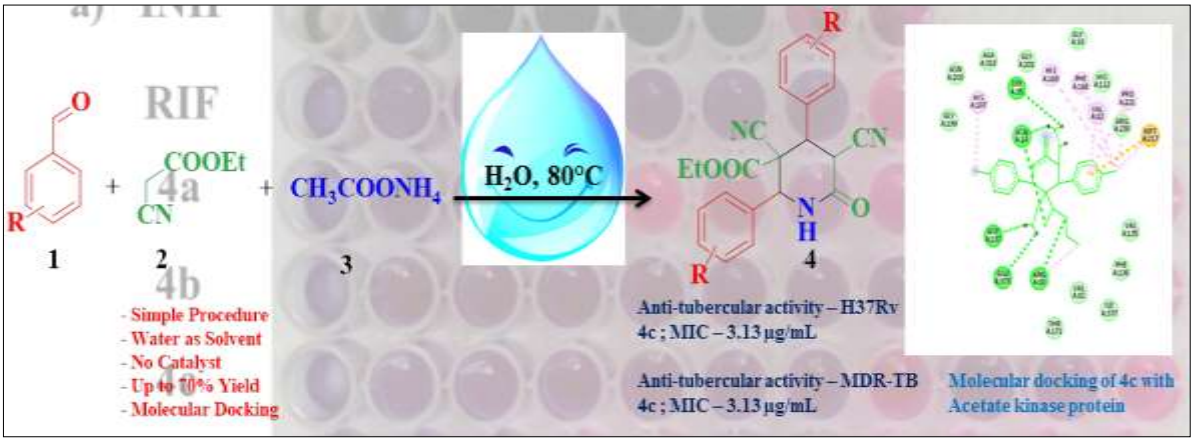

A simple and environmentally friendly one-pot synthesis has been developed for the synthesis of piperidinone derivatives from reaction of ethyl cyanoacetate, ammonium acetate with various aryl aldehydes in aqueous medium. The compounds were screened for antibacterial activity and tested compounds showed moderate antimicrobial activity. Further, piperidinone derivatives were screened for antitubercular activity against *Mycobacterium tuberculosis H37Rv control strain* and *multidrug resistant Mycobacterium tuberculosis* MDR-TB isolates by REMA method. Among the three tested compounds, **4c** showed an excellent antitubercular activity against *H37Rv*and MDR-TB isolates with MIC 3.13 µg/ml. Further docking analysis of synthesized piperidinone derivatives with acetate kinase protein shown these compounds interact with the residues that are in the vicinity of ATP binding site, acetate biding site, active site and magnesium binding site. Thus these derivatives can be promising compounds for antitubercular activity to combat tuberculosis.

Novel carbazole tethered acrylamide/acrylonitrile: synthesis, structural, biological, and density functional theory studies

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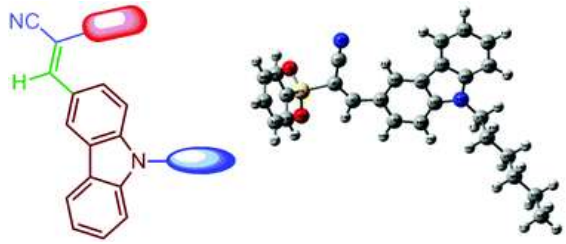
Cancer being the dreadful and most prevalent disease worldwide which needs to be treated in early stage. It is anticipated that global death toll from cancer is progressing to increase (approximately 12 million deaths by 2030). In particular, the fatal rate due to pancreatic cancer is found to be reasonably higher due to its chemoresistence and high invasive nature. In this regard the planar, polycyclic, and aromatic carbazoles are found to exhibit anticancer activity through DNA intercalation or inhibition of DNA-dependent enzymes, such as telomerase and topoisomerase I/II. A series of novel carbazolylacrylamides/acrylonitriles **6a–6h** were synthesized and their structures were established using various analytical, spectroscopic, and single-crystal X-ray diffraction techniques. The antioxidant evaluation of the target chemical entities **6a–6h** was conducted by the DPPH method. The carbazolylacrylonitrile **6h** displayed 65.7% radical scavenging activity (IC_{50} value, 65.08 μM) with respect to standard ascorbic acid. The *in vitro* cytotoxic activity studies revealed **6e** and **6h** as promising anticancer molecules against a human pancreatic cancer cell line, *i.e.*, AsPC1. Density functional theory studies of a model chemical entity **6g** were performed and the results obtained were compared with those obtained experimentally. The appropriate structure, the corresponding bonding features and the vibrational frequencies for the molecule **6g** were determined by employing the DFT-B3LYP method with the 6-311++G(d,p) basis set. The vibrational frequencies of the carbazolylacrylonitrile **6g** calculated theoretically were found to be in good agreement with the corresponding experimental results. In addition, the chemical shifts of ^{1}H and ^{13}C of **6g** were computed by the gauge independent atomic orbital (GIAO) method and compared with the experimental ones.



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Synthesis of New Cyclazines and 4,5-Diaryl-1*H*-pyrrol-3(2*H*)-one unit in Discoipyrroles from Indolizinone-DMAD Cycloadducts

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A synthetic strategy that affords 3',8a-dihydrocyclopenta[*hi*]indolizin-8a-ols and 1*H*-pyrrol-3(2*H*)-ones using cycloaddition of indolizinones with DMAD as the key step is discussed (figure 1). These products arise either through [4+2] or [8+2] mode of cycloaddition of DMAD with the indolizinone moiety.[1] Systematic study on the effect of substituents on the distribution of products showed that electron donating substituents on the C_3-aryl ring favors azatricycle formation. 1*H*-pyrrol-3(2*H*)-ones arising through retro-Diels Alder pathway turned out to be suitable intermediates for the total synthesis of Discoipyrrole C and its analogs.[3] These are alkaloids with proven activity against lung cancer cells[4]. Synthetic details and mechanistic insights will be discussed during this presentation.

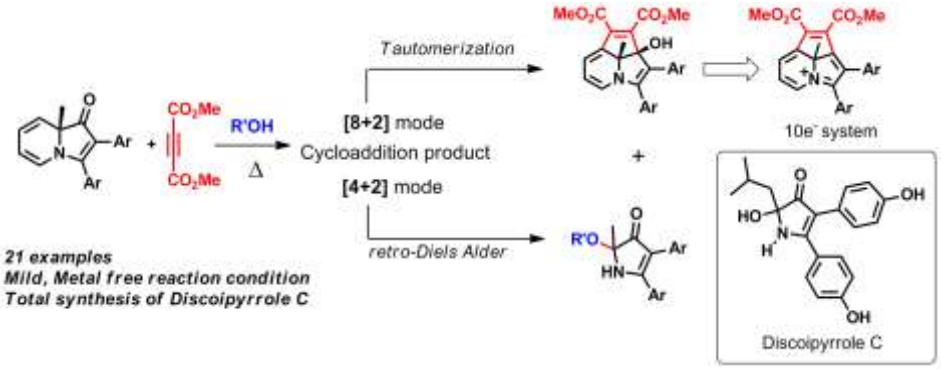

Figure 1. Synthesis of 3',8a-dihydrocyclopenta[*hi*]indolizin-8a-ol and 1*H*-pyrrol-3(2*H*)-one from indolizinone and dimethyl acetylenedicarboxylate *via* [8+2] or [4+2] modes of cycloaddition.

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Sustainable Strategy for C-S Bond Formation Reaction in Organic Synthesis

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C-S bonds are ubiquitously found in natural products. Many organosulfur compounds are widely used in medicinal, pharmaceutical and functional material science. Therefore, the strategies towards making C-S bond formation reactions have become significant in organic synthesis. Till date, great developments have been made for erecting the C-S bonds including transition-metal-catalysis, but under metal-free mild condition using sustainable reagent is less explored. In this regard, developments of efficient, direct and environmentally benign synthetic methods are highly desirable.

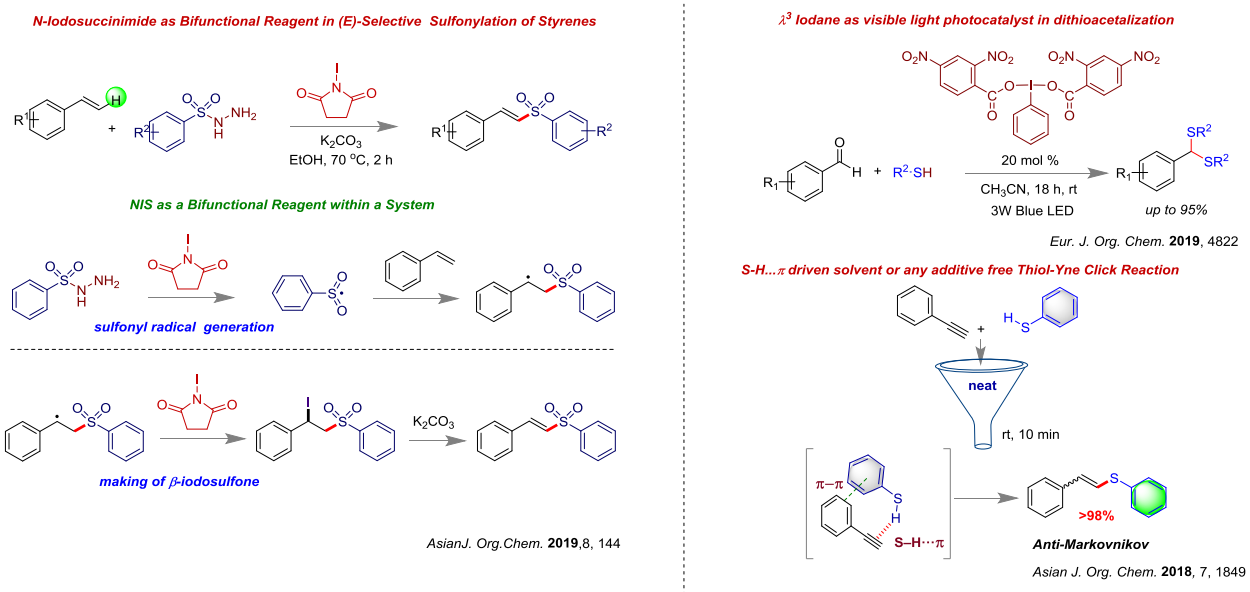

Figure 1.

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Regioselective Synthesis of Isocoumarins via Iridium(III)-Catalyzed Oxidative Cyclization of Aromatic Acids with Propargyl Alcohols

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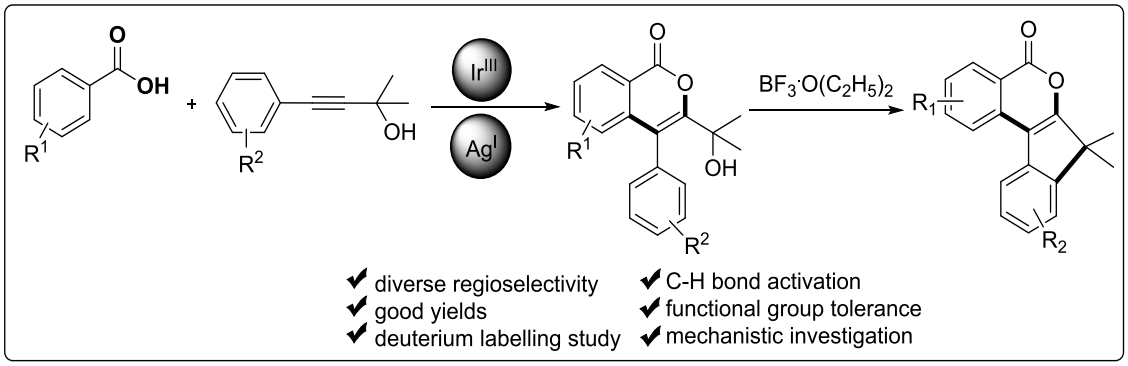
Due Isocoumarins are naturally occurring unsaturated lactones and also the benzo derivative of α-pyranones. Generally, isocoumarins are prepared by the metal-catalyzed cyclization of activated systems like o-haloaromatic esters or acid with π-components, carbonylative cyclization of o-halophenols with πcomponents and electrophilic cyclization of substituted alkynes.[1] Transition-metal-catalyzed oxidative cyclization of substituted benzoic acids with alkynes via C-H bond activation is an efficient method for synthesizing isocoumarins in a highly atom-economical manner. The previously known methodologies in literature using transition metals provided regioisomeric mixtures of isocoumarin.[2] Herein, we have reported an Ir(III)-catalyzed oxidative cyclization of benzoic acids with propargyl alcohols to give substituted isocoumarins in a highly regioselective manner. In the present cyclization reaction, the steric as well as coordinating ability of tertiary hydroxyl group of propargyl alcohol plays a significant role for the high regioselectivity by coordinating with the Ir metal forming a seven-membered metalacycle intermediate. This protocol has broad substrate scope with high functional group tolerance. The observed isocoumarins were also converted into biologically active tetracyclic indeno[2,1-c]isocoumarins[3] by Lewis acid mediated cyclization. A possible reaction mechanism is proposed and strongly supported by the detailed mechanistic investigations and DFT calculations.



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Total Synthesis of Bisindole Alkaloid: Barakacin, its analogues and their biological studies

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Bisindole alkaloids are the interesting class of alkaloids due to their potential applications in medicinal chemistry such as cytotoxicity against cancer cell lines, MRSK PK inhibition, antimicrobial activity, and antifouling activity.[1-2] Barakacin is the first bisindole natural product which has thiazole bisindolylmethane connected hybrid skeleton. Barakacin was isolated from *Pseudomonas aeruginosa* in 2016 by Zendah et al.[3] The same research group revealed its cytotoxic activity against a range of human cancer cell lines. As a part of our ongoing research on total synthesis of bisindole alkaloids, we have achieved the total synthesis of barakacin from readily available and commercially cheap starting materials. The synthesized natural product and its analogues were tested for antimalarial and anticancer activity. The detailed synthetic study, antimalarial and anticancer activity of Barakacin and its analogues will be presented.

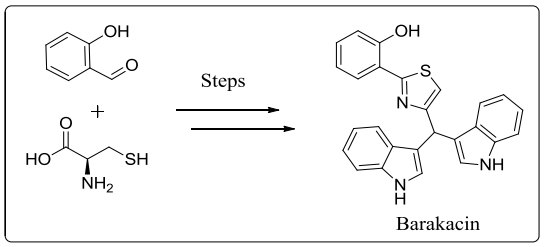

Figure 1. Total Synthesis of Barakacin.

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Green and Sustainable Routes for Key Oxidation Reactions Using Molybdenum Based Metallomicellar Catalyst in Aqueous Medium

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Surfactant based metallomicellar systems are known as efficient catalysts for various organic transformations in aqueous medium.[1] Although oxomolybdenum complexes have vast application in the field of organic transformations due to their efficient catalytic activity,[2] corresponding surfactant based oxomolybdenum complexes are not well established.[3]

In the present study, the use of a surfactant based molybdenum complex (**Mo1**) as catalyst and molecular oxygen from open air as an oxidant has been demonstrated for controlled and selective oxidation of alcohols, amines and tetrahydroquinoline derivatives to corresponding value added products. It is worth noting that the oxidation reactions were carried out in water under the exclusion of extraneous base or co-catalyst. Sensitive/oxidizable functional groups like cyano, sulfide, hydroxyl, phenol, alkene, alkyne and acetal were tolerated during the transformations. Such a high degree of selectivity is attributed to the mildly oxidizing nature of the catalyst. The methodology was found to be worthy for up-scale multi-gram synthesis. We believe that the protocol is likely to find practical use since it employs an inexpensive recyclable-catalyst and an easily available oxidant (under green conditions). The possible mechanistic study has also been proposed based on DFT calculations.

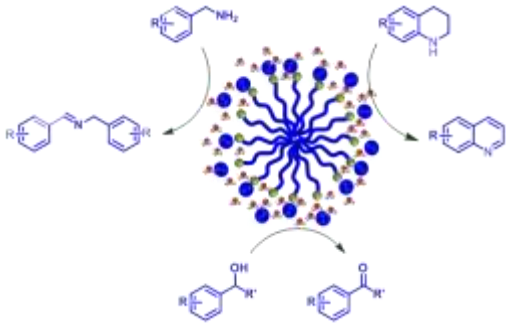

Figure 1. Surfactant based molybdenum complex catalysed oxidation reactions in aqueous medium.

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P-13

Docking studies of thiomorpholine derivatives for PPAR-gamma and AMPK receptors as potential candidates for Type II Diabetes

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As of 2017, according to IDF, about 425 million people have been diagnosed with type 2 diabetes worldwide.[1] Thiomorpholine derivatives have been found to show potent anti-diabetic activity through DPP IV inhibition.[2] In this study, peptide-linked thiomorpholine derivatives (SSP 1 to SSP 30) have been docked against PPAR-gamma complex receptor [PDB Id: 5lsg] and AMPK receptor [PDB Id: 2v8q] to compare with **Sitagliptin** as standard molecule using AutoDock 4.2v tools. Out of these, 16 molecules were found to have better docking score (docking score from -11.18 to -8.58) than the standard Sitagliptin having docking score -7.95 and kI value as 1.5 uM for receptor PPAR-gamma. As for receptor AMPK, 14 molecules have higher docking scores (ranging from -6.06 to -7.41) than the standard (docking score= -5.99; kI= 40.19 uM). Upon analysis of all the test molecules, SSP 17, with a docking score = -11.18 and kI= 6.35 nM, was the most promising candidate for PPAR-gamma and SSP 14, with a docking score of -7.41 and kI= 3.68 uM, as a potential candidate for AMPK receptor. Interestingly, molecules such as SSP 1,6,7,8,14,21,25 and 28 were found to show better potency than the standard in both receptors. Further, the selected molecules underwent ADME studies and all of them were found to follow Lipinski's rule of five. Hence, the 8 subject molecules have potential value for further research towards Diabetes through *in vitro* and *in vivo* studies.

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P-14

Bioavailability - A Critical Parameter in Drug Design and Development

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Bioavailability is a subcategory of absorption and is the fraction of an administered dose of unchanged drug that reaches the systemic circulation which is one of the principal pharmacokinetic properties of drugs. It is an important criterion for therapeutic drug design which is based on several factors like physico-chemical properties (Solubility, stability, pH, isosterism, chirality, etc), first pass metabolism, efflux transporters, protein binding, etc. The bioavailability is on alarm when there is change in the isomer to other form in a racemic mixture where one of the isomers is active. The NME (New Molecular Entities) discovered today mostly have low solubility and high permeability which are classified according to BCS class 2 are in need to apply the numerous approaches in improving their stability, physicochemical properties of poorly water-soluble drugs which directly or indirectly augment their bioavailability. In addition to that the lead structure must be optimised as described by Lipinski rule of Five (Ro5) for drugability of orally actively drugs, similarly application of Lipinski rule for CNS (RoCNS) drugs have been of great interest. The drugs that conform to the Ro5 tend to have lower failure rates during clinical trials. The increase in bioavailability reduces the dosage of the drug administered which is economic to the patients. In recent years bioavailability has become the centre of attraction in drug discovery and development process.

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Liquid–Liquid Extraction of Drug Molecules using Ionic Liquid Based Aqueous Biphasic Systems

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Aqueous biphasic system (ABS) that is a category of liquid-liquid extraction (LLE) has gained considerable importance as replacement of using volatile organic solvents in the extraction of various bioactive compounds [1]. The main benefit of using ABS is that it composed of two water soluble solutes that separate into two co-existing phases at their optimum concentration. Since major constituent is water ABS are more biocompatible and also provides benign media for extraction [2]. In the formation of ABS ionic liquid (IL) played an important role as phase forming promoters, which facilitates the tuning of the polarities and affinities of co-existing phase, which further helps in enhancing extraction efficiencies [3]. In this context, we proposed ABS based on monocationic and dicationic ionic liquids (MILs and DILs) and scrutinized for their ability to extract model non-steroidal anti-inflammatory drugs (NSAIDs). To date, active research has been done on MILs, and its properties and applications have been extensively studied. On the contrary, not much research was done on DILs, which composed of two cationic groups linked by a rigid or flexible spacer with counter anions [4]. In this work, we synthesized imidazolium, pyrrolidinium, morpholinium, and ammonium-based MILs and corresponding DILs with bromide as common anion. The ability of synthesized ILs to undergo phase separation was explored in combination with various potassium salts such as K_3PO_4, K_2HPO_4, and K_2CO_3 at 298.15 K and atmospheric pressure. The phase behavior of proposed MILs and DILs was analyzed with the help of binodal curve and tie lines of selected ternary system composed of MIL/DIL, potassium salts and water. The systematic comparison of phase formation by MILs and DILs has been carried out. Further, the extraction capability of the designed ABS was evaluated for NSAIDs by using UV-visible spectroscopy. The proposed MILs and DIL based ABS showed appreciable ability to undergo phase formation as well as to extract the pharmaceutical compound of interest.

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Fused thiazine and amide tethered dihydropyridines: Design, synthesis, biological evaluation and molecular docking studies

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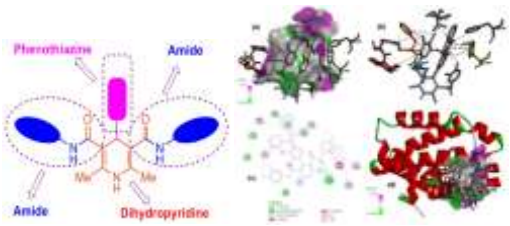
Cancer, a type of inflammation, is the second leading origin of death in the world. There are 9.6 million fatalities around the globe in 2018 due to life threatening diseases and one in six is because of the same. It is anticipated that global death toll from cancer is progressing to increase (approx. 12 million deaths by 2030). Specifically, the rate of death because of pancreatic cancer is found to be plausibly higher due to its high invasive nature and chemoresistance. It has been reported that in United States, the pancreatic cancer is the fourth leading cause for cancer death. Although various types of treatments are available for cancer, the treatments can cause one or more side effects. Numerous drugs are commercially available to treat cancers. Unfortunately, almost all of them are associated with serious side effects; consequently, it is a challenging task to save lives. The rising death rate every year, because of cancer, has made obvious that there is an immediate need for development of newer anticancer agents that can abolish cancer cells with no harm to regular tissues. On the other hand, one of the vital targets of organic synthesis is the rapid assembly of diversified molecules which is a key paradigm of recent discovery of drugs and, multi-component reactions (MCRs) are one of the categories of approach which address this challenge. Dihydropyridine, amide and fused thiazines, phenothiazines are vital structural components with widespread biological profile. Having all the above in mind, a series of novel phenothiazinyldihydropyridine dicarboxamides has been synthesized by adopting a multi-step synthetic strategy and characterized through physical and spectral techniques. Anticancer evaluation has been done using pancreatic cancer cells such as SW1990 and AsPC1 which revealed that meta- and para- chloro substituted molecule 7a exerted the best activity. Also, an appreciable binding affinity (-8.10 Kcal/mol) has been observed during molecular docking between B-cell lymphoma with 7a. Structural diversifications of the potent chemical entities besides further exploration in connection with biological profile of the same are under the way.



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Copper at Air-Water Interface: Technology for Reducing Drug Consumption

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Consumption of purified water is essential for healthy living, however owning a personal water purification unit is not usual for many families in underdeveloped and developing countries. Community water purification plants are the go-to points for fetching purified water by many people. Storage of water is a common practice for eventual uses. However, microbial growth in stored water is inevitable, especially in unhygienic environment.[1] Global loss of 2.2 million human lives per annum in connection with unsafe drinking water and hygiene-related diseases is a disturbing statistic.[2]

The use of copper metal and its ions as disinfecting materials have been well known since ancient time and practiced by many.[3] Dankovich *et al*.[4] coated copper nanoparticles on paper filter and used the coated filter as an efficient material for water purification. In this work we developed easy methods to coat cuprous oxide or copper on buoyant-jute stick pieces (JSP an agricultural waste). The antibacterial potential of copper and the floating nature of the selected variety of wood were found to be an effective combination for safe storage of purified water with respect to prevention of aerial contamination (Figure 1). The material developed being inexpensive and the leaching being below permissible level, we anticipate ample practical use of this finding. This finding also hold potential to bring down the medicine consumption and fatal rate in underdeveloped and developing countries by killing the contaminating microbes at air-water interface.

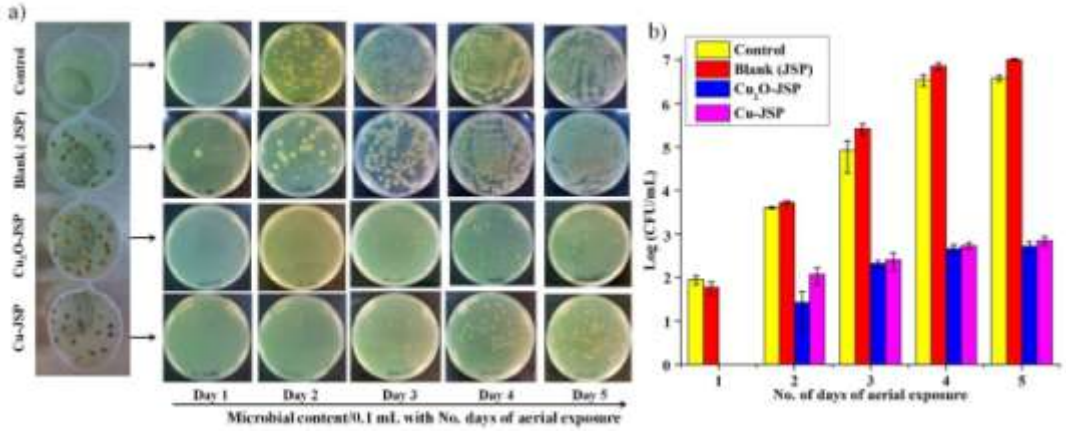

Figure 1. Activity of Cu_2O–JSP and Cu–JSP at air-water interface: (a) Nutrient agar plate showing microbial content in 0.1 mL of each water sample at time interval of 24 hrs. (b) Variation in CFU/mL in control, blank and test sample with increasing numbers of days of aerial exposure.

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Metal-Mediated Carbene Transfer Reactions to Synthesize Medicinally Important Organic Heterocycles

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Heterocyclic derivatives have been found to occur widely in nature and have attracted the attention of chemists and biologists due to their varied nature of physicochemical and pharmacological properties. The indole derivatives are an important moiety of many natural and synthetic molecules with significant biological activities. Arbidol, Indomethacin, PD-0298029, Reserpine, Iprindole and Dimebon are few examples of Indole derivatives showing biological activity.[1] The synthesis of indole derivatives has been the topic of research for over 130 years, and a lot of synthetic methods have been discovered. Our synthetic routes using air stable first-row transition metal complex [M(L)n(L')] (L, L' = ligands) that mediates transfer of functionalized carbene moiety from precursor diazo-compounds to heterocyclic compounds resulting in either C-H bond functionalization at C-3, C-2 positions or cyclopropanation. Using this cost economic complex as a catalyst with low catalyst loading and short reaction time in commonly used solvents afforded products in good yields stereo selectivity. This synthetic routes show that the much explored and expensive heavier transition metal complexes can be replaced by this transition metal complex.[2]

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Theoretical Investigations of Metal-Carbene Intermediates: Implications on Mechanism and Reactivity

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The complex with general formula (L)Ni-PPh_3 (**1,** L = (E)-2-((3-methoxy-2-oxidobenzylidene)amino)-4-methylphenolate) was synthesised, characterized and shown to act as a catalyst for C-H functionalization and cyclopropanation reactions.[1] Theoretical calculations were performed on intermediates with general formula (L-Me)Ni-CR_2 (**2 – 10**, R = H, ester, Ph, Me etc.) at BP86/def2TZVPP level of theory, to understand and compare the bonding situation with that of the parent complex, **1**. Importance was given on predicting which intermediate complexes would be facile enough to undergo C-H functionalization or cyclopropanation by considering their HOMO-LUMO gap (Fig 1) as a parameter for it has direct implications on the mechanism and reactivity. The substrates (substituted indoles, pyrroles, furoates and benzofuran) were also optimised and subjected to MO analysis at M06/def2TZVPP level of theory. It was found that the preference for either type of reactions was dependent majorly on how the substrates presented themselves to the carbenoid intermediates i.e. the fate of the substrate after reaction was predisposed in their frontier MOs.

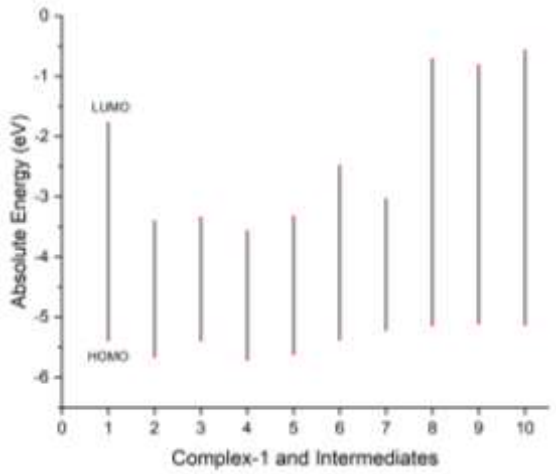

Figure 1. HOMO-LUMO gap (in eV) for species **1** – **10.**

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Metal Mediated Carbene Transfer Reaction-Characterization and Theoretical Study on the Bonding and Stability of Catalyst and Intermediates

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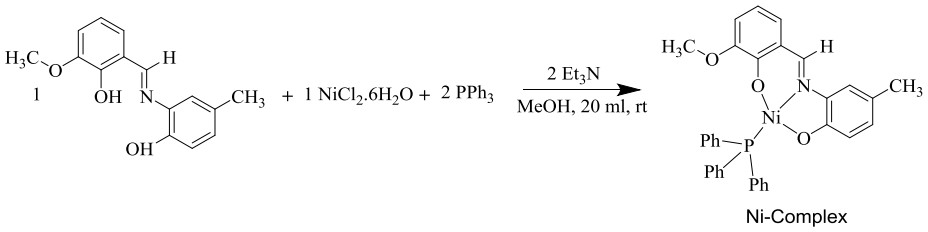
Tetra coordinated Nickel complex of general formula (L)Ni(PPh_3) (L = (E)-2-((2-hydroxy-3-methoxybenzylidene)amino)-4-methylphenol) has been synthesized and characterized with spectroscopic techniques and Single crystal X-ray crystallography. The ^{31}P NMR spectroscopy revealed the partial dissociation of PPh_3 and exposing active Ni center. Owing to this nature, the complex has been explored as a catalyst in the synthesis of medicinally important organic heterocycles.[1] Effort had been taken to understand the underlying mechanism and reactivity by analyzing the complex and metal-carbene intermediates with energy decomposition analysis coupled with natural orbitals for chemical valence (EDA-NOCV), AIM analysis and electrophilicity index. The theoretical results gave deep insight into the structure, bonding of metal-carbene intermediates, while spectroscopic techniques helped in understanding the catalytic activity of the complex.



Scheme 1. Synthetic strategy of (L)Ni(PPh3)

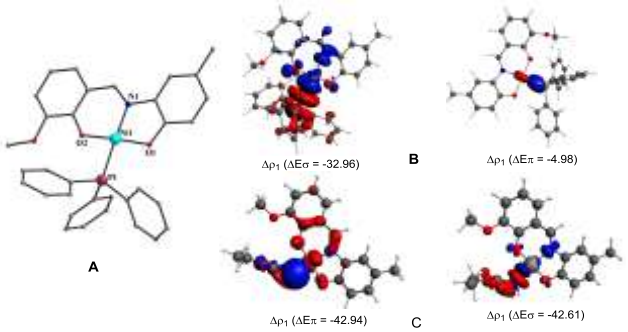


Figure 1. A represents crystal structure of (L)Ni(PPh_3), **B** and **C** represents deformation density plots of the complex and intermediate. Energies in Kcal/mol given in parenthesis.

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P-21

Novel cyanoacetamide integrated phenothiazines: Synthesis, characterization, computational studies and in vitro antioxidant and anticancer evaluations

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Cancer is a leading cause of death around the globe, which claims over six million people died a year and still increasing (WHO). Phenothiazine ring systems are one of the most abundant ones and becoming precious molecular scaffold in medicinal, industrial and academic fields. As an example, Chlorpromazine, a derivative of phenothiazine has been used to treat psychotic disorders and allergy. We designed phenothiazine based cyanoacetamides as a new class of anticancer agents. A series of novel phenothiazine based cyanoacrylamides have been synthesized from phenothiazine through multistep synthetic strategy. The structure of novel molecules has been determined by FT-IR, ^{1}H NMR and ^{13}C NMR spectral techniques. Computational studies were carried out for the synthesized compounds using DFT method with B3LYP/6-311G(d,p) basis set. The target molecules have been screened for their anticancer activity against pancreatic cancer cells. All the synthesized compounds displayed significant invitro anticancer activity against the pancreatic cancer cells AsPC1 and SW1990. Particularly, the compound 6c exhibited the highest activity among the molecules tested against the screened cells. Structural diversification of the potent molecule and screening against other cancer cells are under progress.

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Oxanorbornane Based Anionic Amphiphiles for Transdermal Drug Delivery

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ADMET issues during drug development can be addressed to a large extent using efficient drug delivery systems. Although different types of drug carriers such as polymers, lipids and dendrimers are available, those based on lipids offer several advantages. Fine tuning of aggregation, drug loading and release profile by structure optimization is certainly an important aspect in this regard.[1] As part of our interest in this area, we are involved in design of new amphiphiles using oxanorbornane-based polar head group.[3] Recently, we have extended this concept to access new anionic lipids which can entrap drugs. Details of their synthesis and results from drug delivery studies will be the focus of this presentation.

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Vinylogous Annulation Cascade toward Stereoselective Synthesis of Densely Functionalized Indanones

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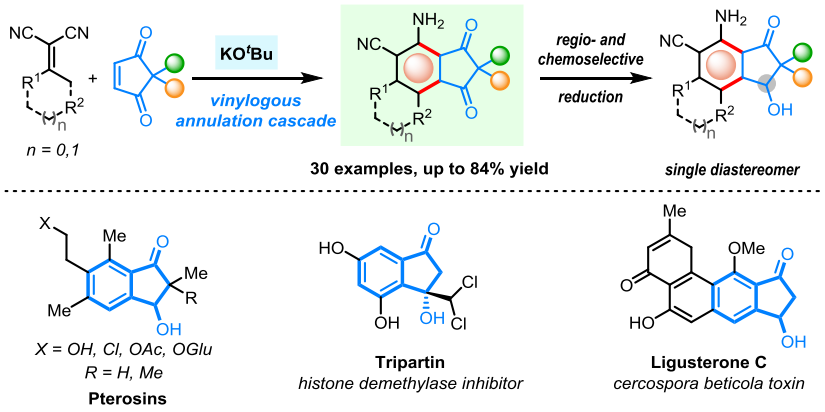
Indanones and their derivatives, particularly 3-hydroxy indanones are valuable benzofused carbocyclic compounds that are ubiquitous in various natural products and biologically active molecules including clinical drug candidates.[1] They also serve as important building blocks to construct different heterocyclic frameworks with increased molecular complexity.[2] The invention of practical synthetic strategies toward this high-value synthon has long been a challenge for organic chemists. Herein, we present a protocol based on vinylogy concept.[3] In presence of a base, for example KO*t*Bu, the vinylogous annulation cascade reaction between alkylidene malononitriles and cyclopentene-1,3-diones proceeds smoothly and products thus formed were chemo- and stereoselectively reduced to deliver densely functionalized 3-hydroxy indanone scaffolds in high yields with excellent diastereoselectivity.[4] The protocol is scalable, displays very broad substrates scope including late-stage functionalization of bioactive estrone, applicable to activated coumarin system, and suitable to access indenoquinoline derivative.



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P-24

In Silico Design, Synthesis and Study of Some Novel N-Substituted Phthalimide Derivatives

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The increasing rate of bacterial resistance to clinical anti-microbial agents and its impact on the treatment of infectious diseases have begun to present a unique problem throughout the world. Phthalimides have attracted tremendous attention in the field of medicinal chemistry owing to their promising biological activities such as Anti- inflammatory, Anti- tubercular, Anti-tumor, Anti-microbial, Anti-viral activities, etc., In view of biological significance and medicinal utility of phthalimide derivatives, the present study involved **"*In silico* Design, Synthesis and Study of some novel N- Substituted Phthalimide Derivatives"**. A series of some novel N-Substituted derivatives were synthesized by condensing Phthalic anhydride with different amino acids, which is followed by condensation with Urea and Hydroxy urea yielded the title compounds. The purity of synthesized compounds were confirmed by Thin Layer Chromatography and Melting point determination. The structure of the title compounds were characterized by FT--IR, ^{1}H-NMR, ^{13}C-NMR and Mass Spectroscopy. Synthesized compound structures were subjected to docking studies using Auto dock 4.2 software against the target enzyme *Glucosamine-6-phosphate synthase* and studied for its *in vitro* anti-bacterial activity against gram positive bacteria (*Staphylococcus aureus*) and gram negative bacteria (*E.coli* and *Psedomonas aeruginosa*) by well diffusion method. All the designed compounds were studied for their Lipinski's rule of five properties and toxicity risk assessment using Molinspiration and OSIRIS property explorer respectively. All the compounds obeys Lipinski's rule of 5 properties. Compound PGU and PGHU showed to be non-toxic and other compounds were reported as unknown chirality. *In vitro* anti-bacterial results showed that compounds PTHU and PLU produced moderate to good anti- bacterial activity and compound PLHU showed good anti- bacterial activity against Pseudomonas aeruginosa compared to standard ciprofloxacin (100 µg/ml).

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Synthesis of Key Intermediates for the Total synthesis of Rhizopyconolides and Related Natural Products

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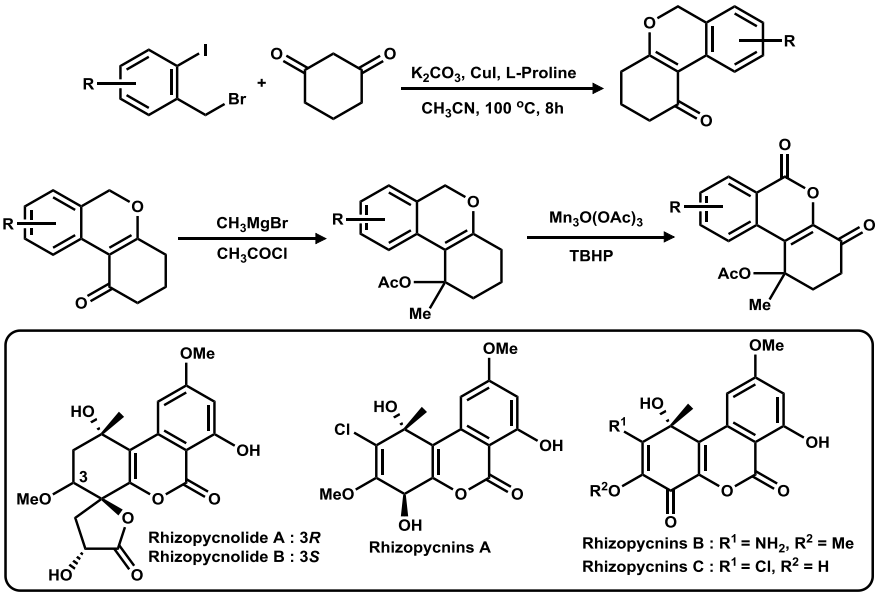
Rhizopycnolides and related natural products exhibit highly potent biological activity. Enantiopure synthesis of these natural products and their analogues is useful for medicinal chemistry research. In organic synthesis, C−H activation is an efficient method and gained much attention for the construction of complex molecules and synthesis of oxygen containing heterocycles are very important in the field of medicinal chemistry and drug discovery. As part of our ongoing research, an efficient protocol for the synthesis of dibenzo[*b*,*d*]pyran-4,6-diones key intermediates of Rhizopycnolides has been developed. 2,3,4,6-tetrahydro-1*H*-dibenzo[*b*,*d*]pyran-1-one has been synthesized from the reaction between *o*-iodobenzylbromide with cyclohexane-1,3-dione using copper iodide through a domino nucleophilic substitution and C-H activation strategy. In present investigation, the reaction is carried by using different organic ligands. In presence of L-proline the reaction gives higher yields and found to the best. Dibenzo[*b*,*d*]pyran-1-one derivatives further reacted with Grignard reagent and followed by acetyl chloride gave corresponding O-acylated product, this upon oxidation gave dibenzo[*b*,*d*]pyran-4,6-diones in moderate to good yields. Furthermore, the reaction is also successful with various substitutions.



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Ruthenium-Catalyzed Free-Amine-Directed (5+1) Cross-Ring-Annulation towards Phenanthridine Alkaloids

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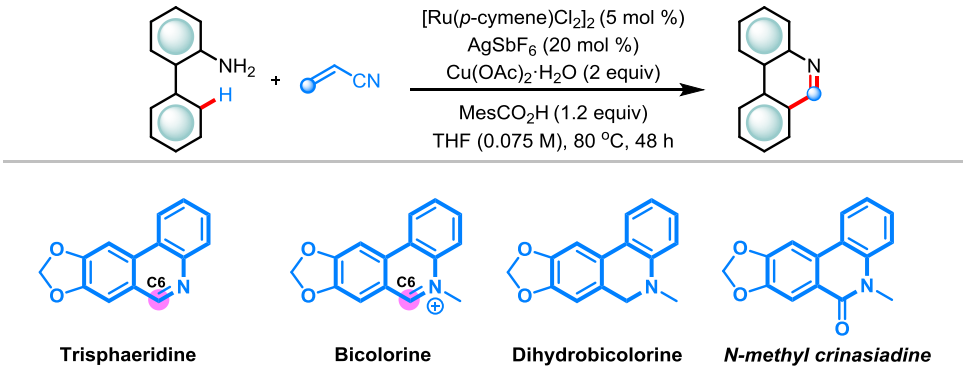
Phenanthridines and derivatives thereof constitute an important class of organic molecules that typicallydecorate the core structure of amaryllidaceae alkaloids.[1] The majority of such alkaloids embrace the 6-unsubstituted phenanthridine moiety and their biological activities range from anti-cancer to anti-fungal, anti-bacterial, to name a few.Traditional synthetic approaches toward such scaffolds typically rely on multi-step processes, often based on radical cyclizations and cross-coupling reactions, and thus, devising a concise synthetic protocol is highly desirable.[2] Herein, we disclosed an unprecedented ruthenium-catalyzed *cross-ring-annulation* reaction of 2-aminobiphenyl with activated olefins *en route* to production of diverse phenanthridine alkaloids in high yields. A combination of C–H activation/annulation/C–C bond cleavage cascade have also been developed to access useful 6-unsubstituted phenanthridine alkaloids like trisphaeridine and bicolorine. Utilization of strongly coordinating free-amine as a directing group for otherwise inert C–H bond activation and identification of acrylonitrile as a suitable one-carbon synthon are very unique in this synthetic endeavor.



Scheme 1: Ru-catalyzed (5+1) cross-ring-annulation approach towards phenanthridine alkaloids

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Optimisation of a Synthetic Scheme Towards Key Building Block for *C*-glycosides of Biologically Active Flavones, Isoflavones and Stilbenes

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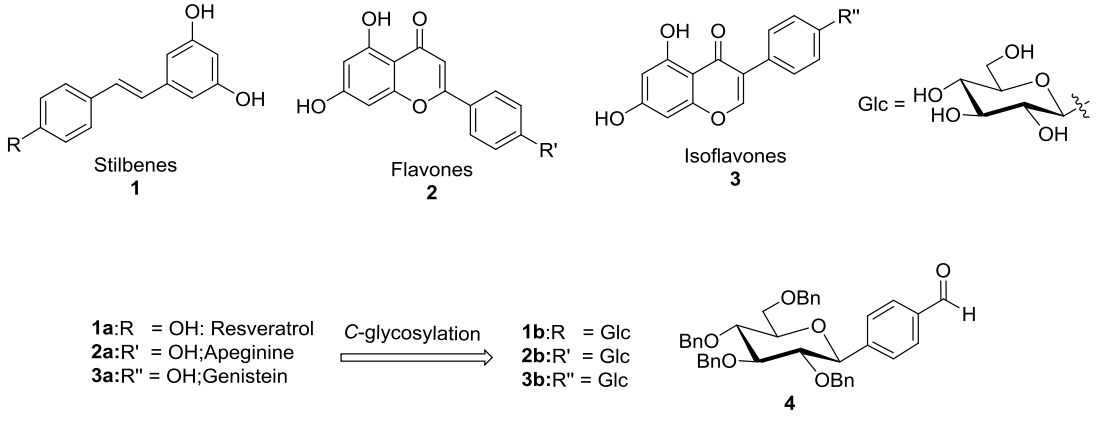
C-glycosides are an important scaffolds in many biological applications such as antioxidant, anticancer and antitumor, anti-inflammatory, anti-diabetes, and antibacterial.[1] Development of new *C*-glucosides through convenient strategies, which provides the target molecule along with its analogues is always an advantage, as it leads to the synthesis of library of potential new compounds. Synthesis of C-glucosides and its analogues using common building is ongoing pursuit in our laboratory. In this context, we are aiming at the synthesis of hitherto unreported 4'-*C*-glucosylated stilbenes (**1b**), flavones (**2b**) and isoflavones (**3b**) in general and 4'-*C*- glucosiode of resveratrol (**1a**), apigenin (**2a**) and genistein (**3a**) in particular. Resveratrol **1a** is a naturally occurring polyphenol presented in lots of dietary substances and used in many biological activities.[2] On other hand, the flavones **2** and isoflavones **3** are also gained the importance in broad spectrum of health-promoting effects and are an indispensable component in a variety of pharmaceutical, medicinal and cosmetic applications.[3] To synthesize the aforesaid targets, we visualized the common building **4**. The incorporation of glucose residue through C-C bond at 4 position of benzaldehyde in compound **4** is the key step in our approach. The optimisation of a synthetic scheme leading to building block **4** will be discussed in the presentation.



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A Novel Synthetic Strategy for the Synthesis of Perlatolic acid

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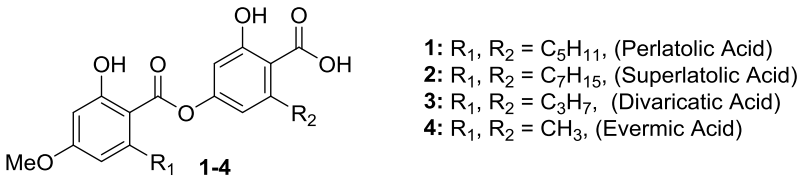
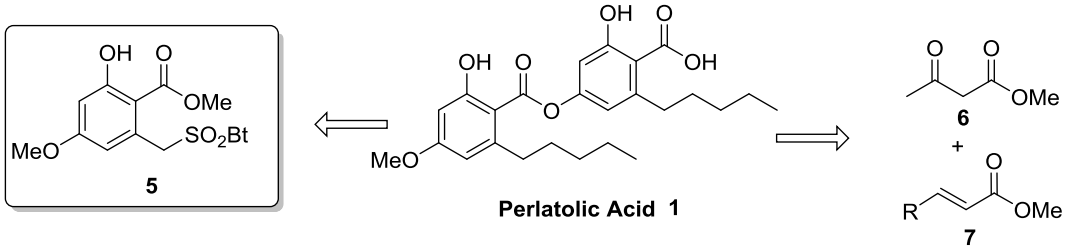
Natural products are resurfacing as important lead molecules in discovery of new drug candidates.[1] Natural products **1-4** are secondary metabolites of lichens. There are reports that these metabolites display diverse biological activities such antimicrobial, antiviral, antibiotic, anti-inflammatory etc. One of the major components of *Cladonia stellaris* extracts [2] is Perlatolic acid (**1**), which amounts to 5 to 11% of the total lichen mass, has attracted attention as anti-inflammatory and neuroactive substance. It is also found to be acetylcholine esterase inhibitor.[3] There are no reports on the synthesis of Perlatolic acid **1** so far. In this context, developing a new synthetic route which will enable access to Perlatolic acid and its analogues from a common building block gains importance. The developed synthetic scheme will also allow the synthesis of other natural products **2-4**. We have visualized synthesis of **1** invoking use of building block **5** [4] developed in our group, which will enable incorporation of an appropriate alkyl residue *ortho* to carboxyl group through Julia olefination reaction. While this is being pursued, another synthetic route banking on condensation reaction between **6** and **7** is also being explored for the construction of aromatic rings present in the target **1**. The synthetic details of these two approaches will presented in the poster.





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P-29

Mechanistic Investigation on the Abnormal Formation of Biologically Active 2-Arylbenzimidazoles from α,α-Diiodo-α'-acetoxyketones

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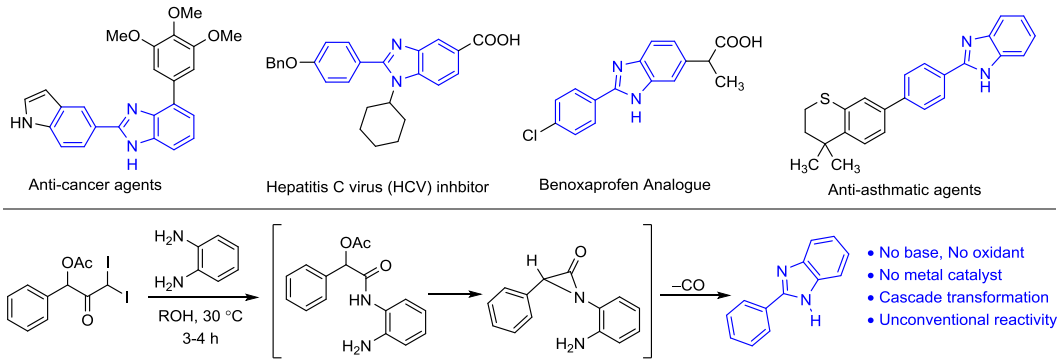
Benzimidazoles are considered as one of the privileged structural scaffolds in medicinal chemistry and drug development, due to their interesting medicinal and biological properties. They have already been used as substructures of many antimicrobial, anthelmintic, antiallergic, and antipsychotic drugs, as well as antiulcer and anticancer agents.[1] Few representative examples of the benzimidazole scaffold based commercial drugs are, nexium, attacand, protonix, prilosec and famvir.[2] Recently we have synthesized a novel class of α,α-dihaloketones i.e., α,α-diiodo-α'-acetoxyketones and employed them as building blocks for the design and development many novel synthetic strategies.[3] In continuation of our efforts towards the exploration of the reactivity of these versatile building blocks, in presence of various Lewis and Brønsted bases, abnormal formation of 2-arylbenzimidazole derivatives has been observed upon reaction with *o*-phenylenediamine. This process found to be very general and efficient. We have performed a systematic study using a series of control experiments to unravel the mechanistic details of this unusual and unprecedented process. The discovery and the detailed mechanistic investigation will be demonstrated in this poster.



Scheme 1. a) Examples of biologically important benzimidazoles, b) Our new strategy for benzimidazole synthesis from α,α-diiodo-α'-acetoxyketone.

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Cu-Catalyzed Synthesis of 2-Acyl-2,3-dihydrobenzo[*b*]thiophenes and 2-Acylbenzo[*b*]thiophenes using Xanthate as Sulfur Surrogate

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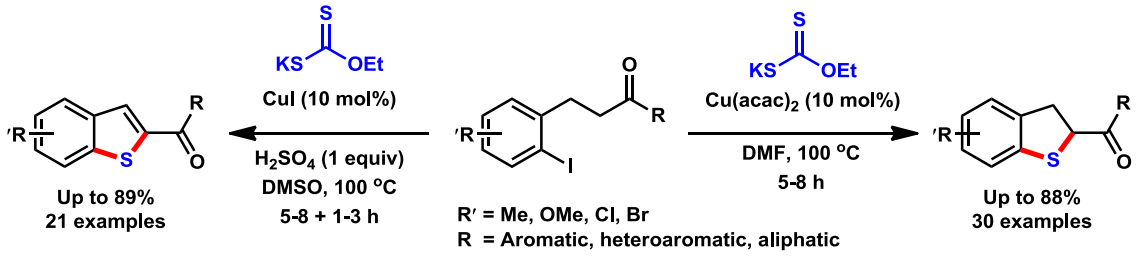
Benzofused sulfur-containing heterocycles are considered to be important due to their presence in natural product and pharmaceuticals.[1] For instance, 2-acyl-2,3-dihydrobenzo[*b*]thiophene core containing Makaluvamine F was extracted from marine sponges, which posed cytotoxic activity against cancer cell.[2] In 2005, Poli *et al*. synthesized enantiopure bis(sulfoxide) and bis(thioether) and used as ligands to form pentacyclic chelated chiral Pd(II) complex.[3] Recently we have developed a domino synthesis for 2,3-dihydrobenzo[*b*]thiophene derivatives have been developed from easily accessible 3-(2-iodophenyl)-1-phenylpropan-1-one using copper catalyst and odourless xanthate as a sulfur surrogate.[4] The methodology proceeds through *in situ* sulfur incorporation followed by $C_{(sp3)}$-H functionalization to generate 2-acyl-2,3-dihydrobenzo[*b*]thiophenes. Further, the domino method has been expanded for the synthesis of 2-acylbenzo[*b*]thiophenes using *in situ* generated halogen from byproduct. Various substituents including halogen derivatives of 2-acyl-2,3-dihydrobenzothiophenes and 2-acylbenzo[*b*]thiophenes can be synthesized in good yields.



Scheme 1. Cu-catalyzed synthesis of 2-acyl-2,3-dihydrobenzo[*b*]thiophenes/2-acylbenzo[*b*]thiophenes

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