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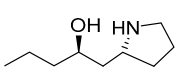
INVITED LECTURE

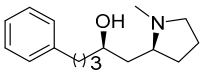
Organocatalytic Approach To Enantiopure *Syn*/*Anti*-1,3-Polyols/1,3-Amino Alcohols/1,3-Diamines: Application to The Synthesis of Bioactive Compounds

Organocatalysis is a rapidly growing research field in organic synthesis and has the advantage of being highly selective and reducing synthetic manipulations.[1] It is often associated with mild and simple reaction conditions that are appealing because of the easy handling, cost and safety issues. The 1, 3-skipped polyol systems with *anti*- or *syn*- configuration are structural units of several natural products including clinically valuable polyene macrolide antibiotics. Similarly chiral 1, 3-amino alcohols and 1, 3-diamines are interesting structural motifs prevalent in pharmaceutical products and chiral core of numerous reagents and also serve as important chiral auxiliaries and ligands for asymmetric synthesis.

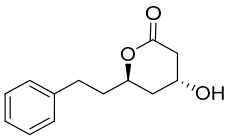
As a part of our research interest in the development of new synthetic methodologies based on organocatalysis and their application to the synthesis of biologically active natural products, [2] we have recently developed new protocols for the synthesis of *syn*- or *anti*-1,3-polyols,[3a] 1,3-amino alcohols[3b] and 1,3-diamines [3c] using proline-catalyzed sequential α-aminoxylation/amination and HWE olefination of aldehydes. We further applied these methodologies for the total synthesis of naturally occurring bioactive molecules such as lactone moiety of compactin and mevinolin, [3d] strictifolione [3e] and passifloricin [3f] and halosaline[3g] etc. The details of these results will be presented.



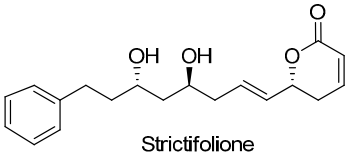
Halosaline



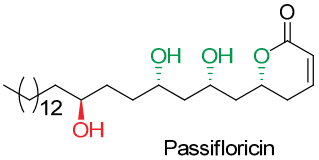
For the treatment of neurological disorders



Lactone moiety of Compactin and Mevinolin (Cholesterol lowering drug)



Strictifolione



Passifloricin

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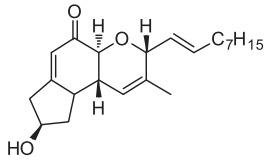
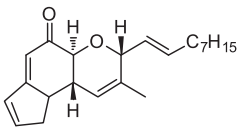
INVITED LECTURE

Novel Synthetic Methods: Towards the Synthesis of Complex Natural Products

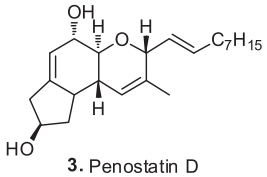
Natural products have inspired chemists and physicians for millennia. Their rich structural diversity and complexity has prompted synthetic chemists to produce them in the laboratory, often with therapeutic applications in mind, and many drugs used today are natural products or natural-product derivatives. Coupled with improvements in approaches for natural-product synthesis, it could be opening the door to a new era in the investigation of natural products in academia and industry. Biologically active natural products often contain particularly challenging structural features and functionalities in terms of synthesis. Perhaps the greatest difficulties are those caused by issues of stereochemistry. Among the heterocyclic compounds, 2,6-disubstituted-5-methyl 3,6-dihydropyrans, are probably one of the most common structural motifs spread across various natural products, from simple glucose to structurally complex secondary metabolites.



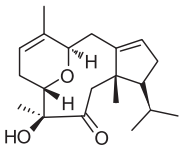
1. Penostatin B



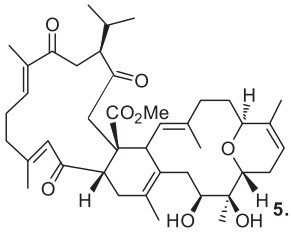
2. *ent*-Penostatin C **(2)**



3. Penostatin D



4.4,5-Deoxyneodolabbeline



5. Methyl Sarcophytoate

During this lecture, we will present the extension of our own developed method of tandem isomerization-intramolecular Hosomi-Sakuari reaction under mild conditions and application towards the synthesis of complex natural products.

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Exploration of Acid-Base Catalysis Concept in Glycosidation

Carbohydrates, the vital endogenous biomolecules, found mostly in conjugation with lipids (to form glycolipids) and proteins (to form glycoproteins), are composed of various monosaccharide units linked together through ***O*-glycosidic linkages**. They serve for storage of energy (e.g., starch and glycogen) and form much of the structural framework of cells and tissues (e.g., cellulose and chitin). Due to high structural complexity involved in the glycoside synthesis by no mean is a simple task. Inspite of the various synthetic methods already developed towards glycoside formation, there is still much need to address the problems associated with stereoselective glycosidic bond formation. Nature follows acid-base catalysis in processing carbohydrates in biological systems. This talk will summarize aspects of bifunctional catalysis used in stereoselective glycoside synthesis. The catalysts used permit hydrogen bond mediated intramolecular SN2-type glycosidation resulting in high anomeric selectivity. The mechanistic details followed by the different catalysts and further application of these methods in the synthesis of complex saccharides will be also discussed.

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1. L. L. Lairson, B. Henrissat, G. J. Davies and S. G. Withers *Annu. Rev. Biochem* **2008**, *77*, 521.
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INVITED LECTURE

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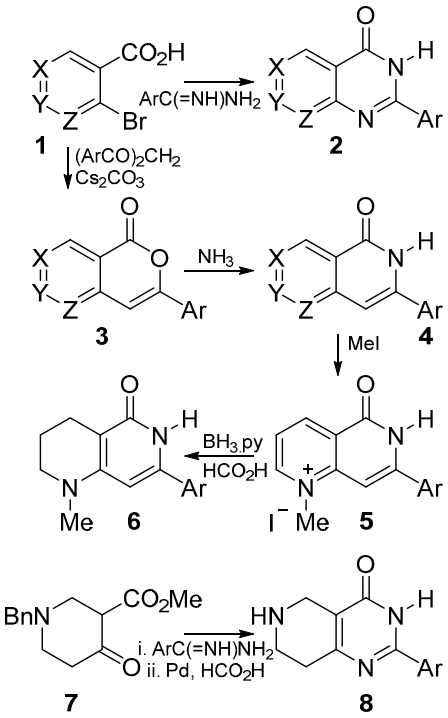
Potency and Selectivity in the Design and Development of New Tankyrase Inhibitors

Tankyrase-1 and tankyrase-2 (PARP-5A and PARP-5B) are members of the poly(ADP-ribose) polymerase (PARP) enzyme superfamily, which modify and regulate target proteins by building poly(ADP-ribose) from the substrate NAD^+ to form short polyanionic polymers [1,2]. The tankyrases have multiple cellular roles, including regulation of elongation of telomeres [3] activation of nuclear mitotic apparatus protein (NuMA) in mitosis [3] and regulation of the *Wnt* signalling pathway [4]. This makes the tankyrases attractive new targets for anti-cancer drug design and development.

We reported, at the previous ISCB conference, our preliminary studies in the design and discovery of 2-arylquinazolin-4-ones and 3-arylisoquinolin-1-ones as potent inhibitors of tankyrase-2. Here we present our development of these compounds and of the aza analogues, the 7-aryl-1,6-naphthyridin-5-ones, 3-aryl-2,6-naphthyridin-1-ones, 3-aryl-2,7-naphthyridin-1-ones, 2-arylpyrido[4,3-*d*]pyrimidin-4-ones, 2-arylpyrido[2,3-*d*]-pyrimidin-4-ones, 7-aryl-2,3,4,6-tetrahydro-1,6-naphthyridin-5-ones and 2-aryl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ones. The isomeric bromopyridinecarboxylic acids **1** were condensed with 4-substituted benzamidines in the presence of CuI and Cs_2CO_3 to furnish **2** (X *or* Y *or* Z = N). The same starting materials **2** also underwent Hurtley couplings with diaryl -diketone enolates; surprisingly, these reactions proceeded more effectively in the absence of Cu to give **3** in good yields. Replacement of the heterocyclic O with N, using NH_3 under forcing conditions, gave the required naphthyridinones **4**. Methylation of the 7-aryl-1,6-naphthyridin-5-ones **4** (Z = N) at 1-N with iodomethane gave the quaternised salts **5**, in which the cationic ring could be reduced with borane to give the tetrahydro derivatives **6**. Compounds **8** were accessed by condensation of the -keto ester **7** with benzamidines, followed by reductive removal of the benzyl protection.



These compounds, the isoquinolinones and quinazolinones were assessed for inhibition of tankyrase-1 and tankyrase-2 and were counter-screened for unwanted activity against PARP-1 and a representative NAD^+-requiring oxidoreductase, IMPDH2. Examples were also evaluated for cytotoxicity against human tumour cells and normal cells *in vitro*. The understanding of the structure-activity relationships was aided by X-ray crystal structures of selected compounds bound into the NAD^+-binding domains of tankyrase-2.

We thank AICR for generous funding.

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INVITED LECTURE

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INVITED LECTURE

Heterogeneous Catalytic Systems for Transformations of Biomass-derived Materials into Value-added Chemicals

1. One-pot Synthesis of Furfurals from Sugars [1]
One-pot reactions using heterogeneous catalysts afford remarkably unique and environmentally-friendly benefits, including avoidance of isolation and purification of intermediate compounds. We have adopted this approach for HMF synthesis from glucose through a two-step reaction in one-pot. Simple use of conventional solid acid (Amberlyst-15) and base (hydrotalcite; HT) afforded the efficient production of HMF. Our strategy involves separating HMF synthesis from glucose into two reactions, (a) isomerization of glucose into fructose catalyzed by solid base and (b) dehydration of fructose into HMF by solid Brønsted acid catalysts. This onepot type catalytic system could be applied to the actual synthesis of furfurals from natural saccharides such as sucrose, cellobiose and lactose or a variety of mixed-sugars including glucose, fructose, xylose, arabinose, rhamnose, raffinose and/or lactose to synthesize HMF, furfural, and 5-methyl-2-furaldehyde.

2. Transformations of Furfurals, Glucosamine and Glycerol into Other Carbonyl Compounds [2]
Furfural could be converted into the corresponding dicarboxylic acid, succinic acid, using Amberlyst-15 as a reusable solid acid catalyst in the presence of hydrogen peroxide in water solvent at 353 K. Fructose is transformed to levulinic acid using Amberlyst-15 catalyst at 373-413 K in water. Fructose is dehydrated into HMF, which is successively hydrated into levulinic acid.

HMF could also be oxidized into 2,5-formylfuran and 2,5-furandicarboxylic selectively by using Ru/HT and Au/HT catalyst, respectively, in the presence of 1 atm molecular oxygen without addition of base. The Au/HT also synthesized α-amino acids from glucosamine-HCl and its derivatives by aerobic oxidation in water solvent. Furthermore, starch-stabilized Pt nanoparticles on HT surface selectively oxidized glycerol in water solvent using molecular oxygen.

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INVITED LECTURE

Ammonium Ionic Liquids as Biocompatible Co-solvents for the Structure and Stability of Biomolecules

We have investigated the biomolecular interactions and related associated structural changes of α-chymotrypsin (CT) with new ILs by using several biophysical techniques including circular dichroism (CD) and fluorescence. The ILs studied in the present study includes diethylammonium dihydrogen phosphate $[(CH_3CH_2)_2NH][H_2PO_4]$ (DEAP), diethylammonium hydrogen sulfate $[(CH_3CH_2)_2NH][HSO_4]$ (DEAS), triethylammonium dihydrogen phosphate $[(CH_3CH_2)_3NH][H_2PO_4]$ (TEAP) and triethylammonium hydrogen sulfate $[(CH_3CH_2)_3NH][HSO_4]$ (TEAS). We observed that all ILs have dominant contribution to the stabilization of the native structure of the CT. Furthermore, the results reveal that phosphate anions of ILs are strong stabilizers and acted as effective refolding enhancers for thermally denatured enzyme structure, whereas the enzyme was not refolded in the sulfate anions of ILs. These findings suggest a new generation of enzyme stabilizers that can be applied to other protein folding studies and biological systems.

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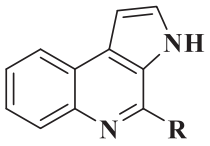
INVITED LECTURE

4-substituted pyrrolo[2, 3-*c*]quinoline Systems: Synthetic, Anti-tubercular and Selective Metal Detection Studies

Resurgence of TB has forced scientific community to look for alternatives to the existing drugs. New chemical entities which are structurally different from the existing drugs can provide an answer to this problem. However this implies lack of control in the hands of the investigator to do a systematic study: to understand either its efficacy or its mode of action. Therefore molecules bearing some resemblance to the existing drugs can be a reasonable starting point for such an endeavour. After exploring the structural similarity of 4-substituted pyrrolo[2,3-*c*]quinoline systems with existing anti-TB drugs isoniazid and ethionamide, we have explored its synthesis and anti-tubercular activity.[1] Though synthesis of [2, 3-*c*] type pyrroloquinoline was known in literature,[2] it was never explored thoroughly due to lack of such compounds from natural sources. Recent spate in literature on natural products containing [2, 3-*c*] type pyrroloquinoline has resulted in a renewed interest in this class of compounds.[3, 4] We have also explored selective metal detection using pyridine substituted pyrrolo[2,3-*c*]quinoline. Results will be presented during the conference.



R = Alkyl or aryl substituents

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Valorization of Waste Feedstocks to Biomedically-Relevant Valuable end Products

The design of benign and environmentally sound methodologies has been the driving force of scientsis in recent years. Attractive and innovative protocols that nowadays are even part of industrial ventures including biomass-derived porous carbonaceous materials, biodiesel integrating glycerol into its composition and more recently gasification and waste valorisation have been recently developed in our group in past years. These topics have extensively covered the preparation and design of (nano)materials and their utilisation in heterogeneously catalysed processes as well as in biomass and waste valorisation practices to valuable products.

In this lecture, we aim to provide an overview of recent efforts from our group on biorefinery concepts entailing waste valorisation of various feedstocks (e.g. slaughterhouse waste, leather residues) as well as algal valorisation to biomedically-relevant high added value products.

INVITED LECTURE

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Natural Polymers in Medical Products: Carboxycelluloses and Their Nanoparticles

Due to its biocompatibility and biodegradability, cellulose and its derivatives have long been used in the medical field as drug delivery materials. Recent researches in nanobiocomposites of cellulose, nanocellulose, and functionalized nanocelluloses have vastly expanded the range of potential applications of cellulose. Especially in the past 2-3 years, nanocellulose with amino and carboxy functionalization have been shown to have exciting properties that can be exploited in the medical field. As is well recognized, controlling the shape, size and surface functionality of nanoparticles can be a potent tool to manipulate the properties, and thereby the applications, of nanoparticles. This paper describes the controlled synthesis and characterization of spherical shaped carboxycelluloses of narrow particle size distribution in the range 25-35 nm, their anti-microbial properties using a wide range of bacterial species. The studies on thermal properties of these nanoparticles for use in nanobiocomposites, and their solubility in aqueous and non-aqueous media is also discussed.

INVITED LECTURE

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Biomedical Application of Oxidized Polysaccharide as a Self-Degradable Material

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Introduction: Cell transplantation serves as an alternativetreatment to whole organ transplantation forfailing or malfunctioning organs.The concept of tissue engineering permits *in vitro* expansion of isolated cells using cell culture techniques and their transplantation for organ regeneration.The material should be biocompatible, non-toxicity and biodegradability. Polysaccharides are natural polymers that include cellulose, chitin, and starch which often be selected to be the scaffold for cell culture. Cellulose is the most abundant polysaccharide found on earth, but cellulose has many limitations in utilization and manipulation such as its poor solubility in water or organic solvent, its solution is highly viscous and present gel formation ability.We found that aldehyde introduced polysaccharide via Malaprade oxidation can be degraded at the glycoside bonds through the reaction with amino groups. In this study, we focus on the control of cellulose scaffolds degradation by oxidation and reaction with amine species.

Experiment: 1-Butyl-3-methylimidazolium chloride, an ionic liquid, was used to dissolve cellulose at 100èC, added NaCl to adjust the pore size of scaffold, maintained at room temperature for 7days, providing flexible cellulose hydrogels. The cellulose scaffold was modified and oxidized using periodate oxidation (Malaprade oxidation), oxidation of carbohydrate by glycol cleavage to provide dialdehyde. Aldehyde groups introduced into cellulose were quantified by simple iodometry. During immersion of the cellulose scaffolds in the amino acid solution, the mass loss of the scaffolds was evaluated.

Results and discussion: Porous cellulose hydrogel scaffold were developed by using ionic liquid as a solvent with NaCl by leaching method. The aldehyde groups were well introduced by periodate oxidation. The introduced aldehyde groups reacted with amino groups to form Schiff base. The cellulose scaffolds after oxidation degraded in the amino acid solution. And the degradation was controlled by increasing the concentration of periodate, time of reaction and concentration of amino acids. Partially oxidized cellulose is the chemical properties of the oxidized residues and, in particular, the hydrolytic lability that may provide a basis for biomaterial with increased biodegradability. The results indicated that 5, 10, 15, 20, 25% oxidized cellulose scaffold completely degraded in 5% glycine within 4, 2, 1, 0.75, 0.5 hours respectively but 1% oxidized cellulose scaffold partially degraded in 16 hours and 0% oxidized cellulose scaffold is not degraded. Successfully we developed the cellulose scaffolds by controlling the degradation.

INVITED LECTURE

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INVITED LECTURE

Supramolecular Chirogenesis in Porphyrinoids and Related Compounds

Porphyrinoids are important and excellent buildind blocks for the assembly of supramolecular nanostructures. They are ideal chromophores due to the specific and highly appropriate spectral, physiochemical properties, facial handling and superior propensity to form various supramolecular assemblies. Cyanuric chloride is an excellent synthon for the preparation of structured multitopic molecules by differential replacement of each chloride by any nucleophiles. The reaction of melamine with cyanuric acid leads to formation of stable H-bonded 2D network. It is possible to control the formation of 2D networks such as linear tape, crinkled tape and rosettes by steric hindrance and substituents both in melamine and cyanuric acids.[1] The reaction of 5-(4'-aminophenyl)-10,15,20-triarylporphyrinato zinc with 2-amino-1,3,5-triazine leads 2-amino-4,6-bis[5-(4'-aminophenyl-10,15,20-triarylporphyrinatozinc]-1,3,5-triazines which form rosettes by hydrogen bonding with 5,5-dialkyl barbituric acids in non-polar solvents.[1,2] Similarly the coordinative and ionic interactions have been used in the self assembly of selected porphyrinoids.[4,5] A smart combination of supramolecular chemistry with chirality in chemistry leads to supramolecular chirogenesis. The asymmetric induction, transfer, amplification and modulation of chiral processes are governed by non-covalent supramolecular forces such as hydrogen bondings, hydrophobic interactions and metal heteroatom bindings.

Anionic achiral water soluble porphyrins have been used to form chiral supramolecular systems by the induction of chiral compounds. The formation of a chiral supramolecular host-guest complex between achiral zinc bisporphyrins and chiral non-racemic guests, the CD response occur in porphyrin spectral regions which are diagnostic of the absolute configuration of chiral guest. Supramolecular chirogenesis is used in the determination of absolute configuration of 1,2-diamines, pharmaceutical agents, synthetic intermediates and natural products. The control of supramolecular chirality in different porphyrionids at various levels is a challenge in the context of molecular self assembly, the design of memory systems, sensors and nanostructure materials.

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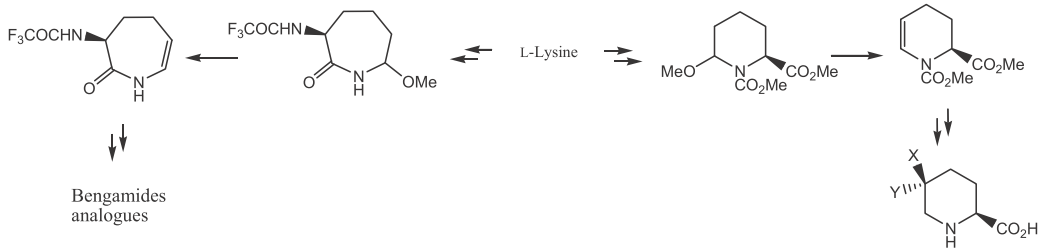
INVITED LECTURE

Electromethoxylation of L-Lysine Derivatives towards Biologically Relevant Natural Compounds and Analogues

Electromethoxylation to the nitrogen atom is a well established methodology for the regioselctive activation and functionalization of azaheterocycles. ˜Methoxy-*N*-acyl moieties obtained by electrochemical oxidation are stable and valuable precursors of *N*-acyliminium ions under acidic conditions. Nucleophilic additions to these highly electrophilic species, also known as amidoalkylations or Mannich-type condensations, are often used to introduce substituents at the -position of the nitrogen atom. On the other hand, these ˜methoxy-*N*-acyl derivatives may lead to the corresponding *N*-acylenamines, *via* acid-catalyzed elimination of methanol. Such *N*-acylenamines are valuable substrates for regioselective functionalization at and positions to the nitrogen atom, *via* diastereoselective electrophilic additions. This talk will be devoted to the reactivity and synthetic applications of *N*-acyliminium ions and *N*-acylenamines derived from L-lysine.



Six-membered endocyclic enecarbamatee were harnessed in the synthesis of new analogues of pipecolic acid,[1,2] while endocyclic enecaprolactams were variously functionalized[3] towards new analogues of bengamides,[4] a class of mixed biosynthetic secondary metabolites isolated from marine sponges.[5]

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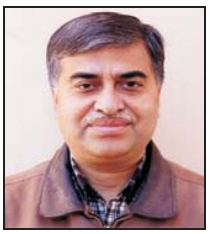

Towards Protection Group Free Step Economical Synthesis of Some Natural and Non Natural Bioactive Polyphenolic Compounds

Environmentally benign chemical practices have provided a fresh stimulus to develop a strategy with minimum number of steps, atom economy and waste minimization besides devoid of protection-deprotection steps. A protection/deprotection event introduces at least two steps into a sequence, incurring costs from additional reagents and waste disposal besides leads to a reduced overall yield. Our group from noticeable time working on such green methodologies for synthesis of various bioactive phenolics like FEMA-GRAS approved 4-vinylphenols, chalcones and stilbenoids etc. Phenolic compounds are characterized by the presence of hydroxylated aromatic ring system and are widely distributed in plant kingdom. Interest in accessing these molecules have gained pace because of plethora of biological activities such as anticancer, antibacterial, antifungal, anti-inflammatory, pesticidal, and antimalarial etc. However, exploration of these compounds is severely hindered by their insufficient percentage in their natural resources besides their tedious synthesis involving protection-deprotection. In this context, natural and non-natural hydroxylated stilbenoids (symmetrical/ unsymmetrical), distyrylbenzene, octupolar stilbenes stilbene-chalcones and stilbene-cinnamate hybrid have been synthesised utilizing microwave and ionic liquid with devoid of protection-deprotection strategy. The details will be discussed during presentation.

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INVITED LECTURE

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Retinoids and Tocopherols in Translational Medicine: Design, Synthesis and Biological Activity of Compounds in Vitamin A and E series

Carotenoids and related linear polyenes like vitamin A are important in control and cure of several diseases like the diseases of the skin, eye, lung, cancer and various other metabolic ailments.[1] Similarly a-tocopherol form of Vitamin E is a well known antioxidant/radioprotective compound, which inhibits lipid peroxidation and other free radical-mediated reactions in biological systems.[2] However, the largely hydrophobic character of these compounds make them poorly soluble in aqueous media, which in some cases, limits their therapeutic efficacy and this has a strong influence on their pharmacokinetic and pharmacodynamic properties. Further, oral administration of vitamin E compounds in biological systems is complex because of its oily nature. Efforts have been made to ameliorate these shortcomings by structural modifications at various positions of the parent molecules. In view of the fact that the phenolic group and the phytyl side chain in vitamin E group of compounds play critical role in their radical scavenging action, we have undertaken design and development of structural analogues of a-tocopherol by modification of its carbon-5a position. In one of our strategies, we have employed click chemistry to design novel glyco-conjugates of a-tocopherol, some of which are solid, and show significant water solubility and radical scavenging activity. The novelty of the synthetic approach lies in the use of glyco-alkynes and tocopherol azide to obtain the glycoconjugates under the click condition.[3] In yet another approach, we have functionalized C-5a methyl group of a-tocopherol to obtain new types of stable thio-a-tocopherols. The novelty of these compounds lies in their bifunctional nature and, hence, enhanced radical scavenging activity.[4] The influence of these structural changes on the dynamics of oxidation products formation has been investigated by DPPH and methyl linoleate peroxidation methods. We have also undertaken ring, chain and end group modifications of retinyl and β-ionyl compounds yielding novel structural analogues of compounds in vitamin A series with interesting anti-radical and anti-cancer activities.[5,6] Details of our efforts towards design, synthesis and bioassay studies together with an overview of the efforts made in the field of vitamins A and E with respect to their potential use in translational medicine and the future outlook on these and related compounds as new therapeutic agents will be discussed.

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INVITED LECTURE

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Radiation-induced Micro- and Nano- fabrication of Polymer-based 3-D Structures for Microfluidics and Lifescience Analytics

The design and the fabrication of lab-on-a-chip microsystems for analytical applications require the development of an extended toolbox including a variety of techniques related to chemisty and material sciences. Radiation-induced polymerization, degradation or grafting can be implemented with a high degree of spatial and temporal control on the chemical elaboration of bricks forming in a step-wise manner highly integrated systems.

The base components consist of pressure resistant and solvent tight microchannels with their associated fluidic connections. Tailored surface treatments as well porous monolithic structures can then be achieved *in situ,* with easy control of the location and of fluidic properties. Particularly, the formation of reactive polymer monoliths starting from monomer dissolved in porogenic solvents represents an attractive way for the preparation of supports for various applications in bio-analytical microsystems. Unit operations such as desalting, peptidic hydrolysis, solid-phase extraction, analyte preconcentration, selective binding and chromatographic separation can be achieved and optimized by virtue of the different degrees of liberty offered by the systems.

The present paper reports on the optimization of photolithographic procedures as well as on our recent advances in this photopolymer-based technology and demonstrates the feasibility of various monolithic phases adapted to the different functions listed above.

Various efficient routes involving UV or EB-polymerization for elaborating microsystems with integrated porous monoliths will be presented. The fluidic behavior of the capillaries or of the microsystem channels can be correlated to geometric, compositional and processing parameters, and therefore adapted to the requirements of the desired analytical applications.

More recent developments in the use of 2-photon photopolymerization for the fabrication of nanostructured surfaces and 3D nanosystems will be also presented.

INVITED LECTURE

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Isocytosines as Novel Xanthine Oxidase Inhibitors

Xanthine oxidase inhibitors are employed in the treatment of hyperuricemia/gout. Its main treatments in market are Allopurinol and Febuxostat. Allopurinol co-ordinates to molybdopterin cofactor and gets hydroxylated unlike Febuxostat which does not show metal co-ordination thus differing in their mechanism of action. A novel scaffold isocytosine was predicted to have 'xanthine-oxidase-inhibition' activity from virtual screening of in-house synthetic library using 'Prediction of Activity Spectra of Substances' (PASS) software. 24 compounds predicted by PASS were docked to xanthine dehydrogenase. 3 compounds scored better than Allopurinol with interactions similar to Febuxostat. In-vitro IC_{50} values were calculated for 24 hits in xanthine oxidase inhibition assay run on high-throughput system. The 3 best docked compounds showed IC_{50} in micromolar range. One of these hits (IC_{50}=9.4μM) was taken as starting point for hit-to-lead studies. Repeated cycles of structure-guided design, synthesis and in-vitro screening resulted in many nanomolar compounds. Plasma pharmacokinetics of some of the potent compounds studied by oral route gave low oral exposure. In-vivo efficacy studies done in hyperuricemic rat model thus resulted in low percent reduction in serum uric acid level. Further attempts were focused on improving the oral efficacy of low-nanomolar compounds through chemical modifications. The best modification was obtained by removal of hydroxyl group from isocytosine moiety that gave vast improvement in PK and ~70% in-vivo efficacy of allopurinol. In summary, concerted modeling and medicinal chemistry efforts resulted in a potent compound with good oral efficacy.

INVITED LECTURE

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INVITED LECTURE

The Development of a New Biodegradable Polymer for Drug-Delivery Applications: From Start to the All to Well-Known Ending

Today nanopartica GmbH is the only commercial producer of dendritic polyglycerol [1] that Prof. Haag, FU Berlin, is working intensively with in his research group since many years. Even though the polyglycerol is an excellent dendritic polymer that can be used also for drug-delivery applications, [2] it lies in our interest to develop a polymer that can be more easily degraded by biological functions.

As a company the starting point of research is slightly different compared to in academia. Before any experimental work is done we always start with scanning through all the patents and articles that exists, and if a big enough gap is found, then we take the decision to step in.

Based on our investigations we therefore started working on a new core-shell hyperbranched polyester composed by an highly hydrophobic core and a hydrophilic shell. The hydrophobic polyester core, give a potentially biodegradable material, indicate to encapsulate hydrophobic drug molecules. In literature there are several examples of biodegradable polymers and one of the most famous and most used biodegradable hyperbranched polyesters is Boltorn® from Perstorp™, that are extensively being used for drug-delivery [3].

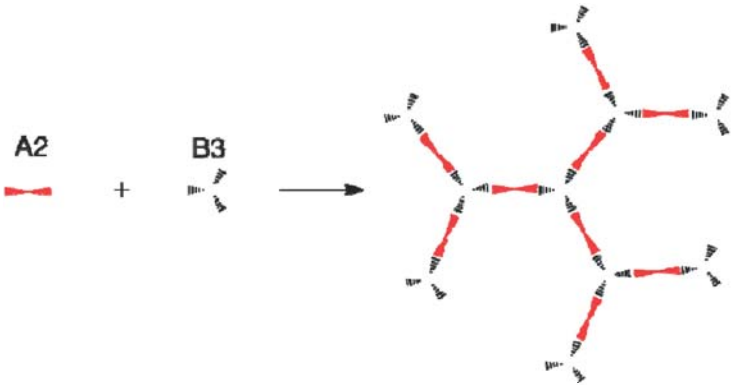

Fig. 1. General scheme of the synthesis of the biodegradable polyester.

The synthesis of the newly developed hyperbranched polyester were fully optimized, and conditions were found to give a broad range of polymer sizes ranging from 4 kDa up to 20 kDa. A hydrophilic shell has been built up on the hydrophobic polyester core and, the host guest capacity of those new nanocarriers, were investigated for drug delivery applications.

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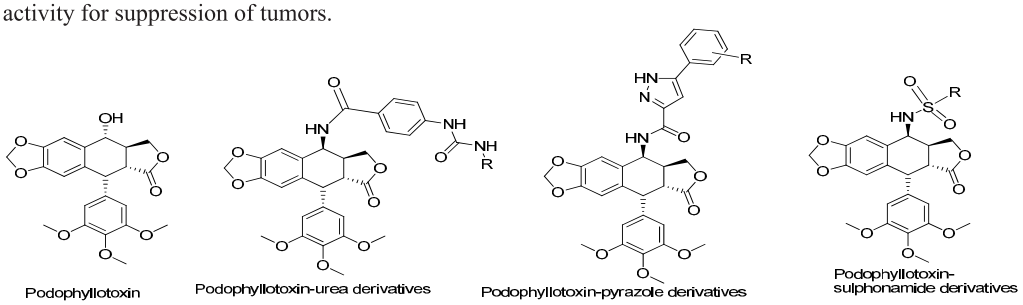
Podophyllotoxin Congeners as Potential Anticancer Agents

Podophyllotoxin (1), a naturally occurring aryltetralin lignan, is extracted as the main component from the roots and rhizomes of *Podophyllum* species such as *Podophyllum hexandrum* and *Podophyllum peltatum*. Podophyllotoxin inhibits the assembly of tubulin into microtubules through interaction with protein at the colchicine binding site, preventing the formation of the spindle. However, its semisynthetic derivatives like etoposide inhibit DNA topoisomerase II (top-IIα). Despite of their wide clinic application, there are several limitations for these semisynthetic podophyllotoxin derivatives, which has inspired to further search for new effective antitumor agents based on this scaffold. Previous structure–activity relationship (SAR) studies suggest that 4β-stereochemistry and 4-N-linkage are the essential structural features for topoisomerase IIα inhibitory activity. These studies prompted us to design and synthesize new congeners of podophyllotoxin by linking this to different heteroaromatic scaffolds at C-4 position as potential anticancer agents with better therapeutic activity for suppression of tumors.



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INVITED LECTURE

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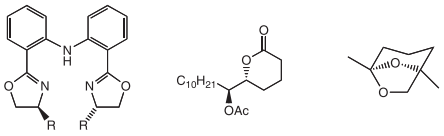
Recent Developments in Catalytic Asymmetric Synthesis

Asymmetric catalysis, one approach for the preparation of enantiomerically pure compounds and the focus of research in both academic and industrial laboratories, is an attractive technology as a small amount of enantiomerically pure material can produce large quantities of enantiomerically enriched or enantiopure material. Research in asymmetric catalysis to date highlights the difficulty in finding a 'universal' ligand suitable for a wide spectrum of reactions and substrates. For this reason the preparation and testing of new ligands for asymmetric catalysis is an active research field.

This presentation will describe the synthesis of C_2- and non-C_2-symmetric analogues of our bis-oxazoline ligands **1** and their application in the Nozaki-Hiyama-Kishi allylation, crotylation, methallylation and homoallenylation of aldehydes, Scheme 1.[1-3] In addition, the products of homoallenylation (-allenols) will be tested as substrates for a series of reactions in order to study their usefulness in synthetic chemistry.[4]

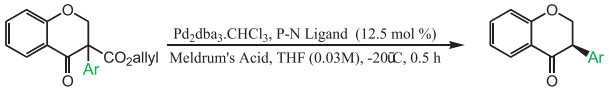
The asymmetric synthesis of, among others, pheromone **2** and (-)-frontalin **3** will also be discussed, Scheme 1.[5-6]



1 **2** **3**

Scheme. 1. Ligands and target molecules to be discussed.

We recently developed the first catalytic asymmetric synthesis of isoflavanones, a group of natural products of generic structure **4**, which exhibit interesting anti-fungal and anti-bacterial activity in addition to behaving as potent phytoalexins. This presentation will describe our work on the application of palladium complexes of phosphinamine (P-N) ligands to catalyse an enantioselective decarboxylative/protonation of -keto esters **5** to form the -aryl-containing isoflavanones **4** and their biological evaluation, Scheme 2. [7]



5 **4**

Scheme. 2. Preparation of isoflavanones **4** by enantioselective decarboxylative/protonation.

Our studies on the application of this protocol to the preparation of naturally occurring examples Sativanone and 3-*O*-Methylviolanone and also be presented

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INVITED LECTURE

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Transition Metal-catalyzed C- H Functionalization and Tandem Reactions for Synthesis of Imidazo[1,2-*a*]pyridine Based Heterocyclic Compounds

In recent years, there has been enormous development on transition metals catalyzed direct C- H activation and functionalization processes that feature atom economy and avoids pre-functionalization of substrates.[1, 2] The direct transformation of C–H bonds provides shortcuts compared with classical organic synthesis, thus rendering synthetic routes more straightforward and atom-economical. The challenge now is to extend the ability of these processes to generate a large number of structurally diversified compounds. Encouraged by the growing demand for environmental friendly and economical protocols for the synthesis of complex molecules, we explored transition metal catalyzed C–C and C–N cross coupling reactions based on C–H bond activation for the synthesis of novel heterocyclic compounds.[3, 4] The lecture will highlight recent methods developed in our group for imidazo[1,2-*a*]pyridine and fused imidazo[1,2-*a*]pyridine derivatives using transition metal-catalyzed C- H functionalization and tandem reactions involving azide-alkyne cycloaddition, C- N coupling and intramolecular coupling reactions.

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INVITED LECTURE

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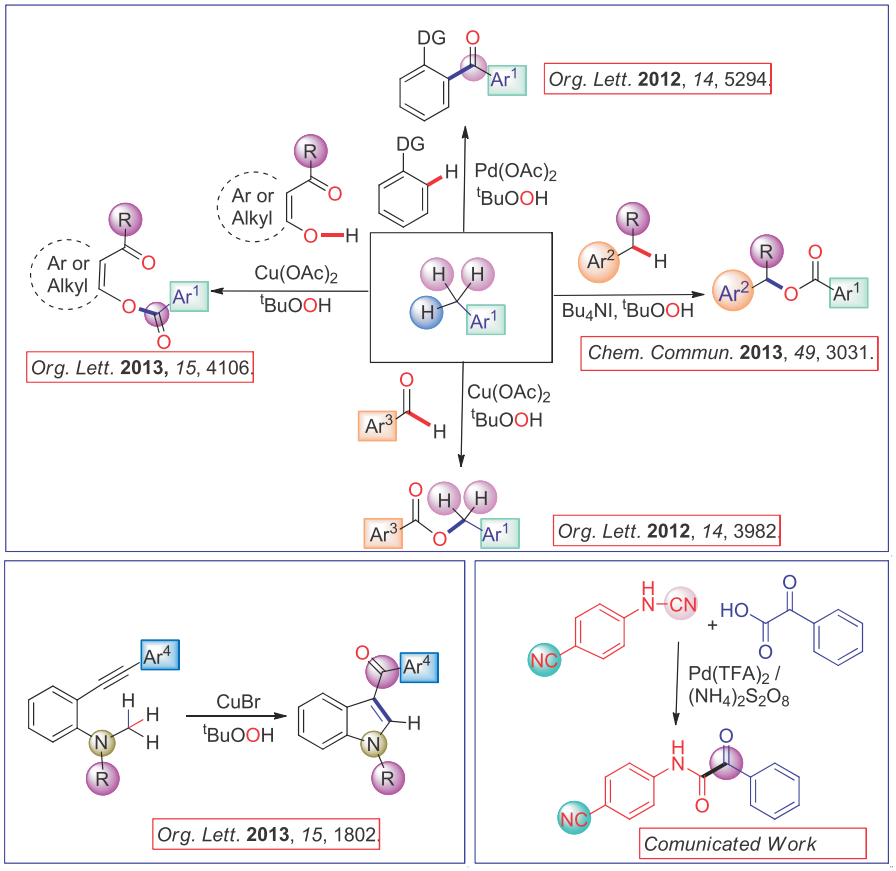
INVITED LECTURE

Unpredictable Coupling Reactions

Alkylbenzenes (Ar-CH_3) are no more inert, of late they have been sources to ArCO, $ArCH_2$, ArCOO as depicted below. Works pertaining to this and some others on unconventional coupling shall be presented during the talk.



Acknowledgments: I sincerely thank all my students for their invaluable contributions to the work described in this talk and I also thank DST, CSIR for financial support.

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Optical Limiting Performance of Donor-Acceptor Molecular Systems

Donor-Acceptor molecular systems are found to be potential candidate for Photonic and electronic applications.[1] The fast development of laser technology in various applications has led to the need for materials, which can protect the sensors and eyes from the hostile laser light. Optical limiters are materials that are transparent at normal light intensities, but opaque to very bright light. The materials used for optical power limiting are fullerene, Porphyrins, Pthalocyanines and organometalic compounds.[2] Molecular modifications are commonly adopted to improve their optical limiting properties.[3] In this presentation, I will discuss about the design and synthesis of Donor-acceptor molecular systems and their optical limiting behavior.

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INVITED LECTURE

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Asymmetric Vinylogous Reactions: A powerful Tool for Creating Functionalized Framework

The 2-silyloxy dienes obtained from furan, pyrrole and thiophene have emerged as a powerful synthons. Particularly, 2-silyloxy furans useful in accessing γ-butenolides and γ-lactone frameworks have been extensively explored in the total synthesis of natural products and biologically active molecules. These heterocycles behave as a vinylogous nucleophile and after reaction with carbonyl and carbonyl derived compounds (aldehydes, ketones, aldimines, ketimines, enals, enones, and heteroatom-stabilized carbenium ions) offer a multitude of highly functionalized structures.[1] Also it grants a synthetic track, where a number of functional group and selected stereochemistry can be established. In this presentation, some recent developments of asymmetric vinylogous Mukiyama Michael reaction[2],[3] and the vinylogous Mannich reaction of 2-silyloxy furans in my laboratory, will be discussed.

A highly diastereo- and enantioselective organocatalytic asymmetric vinylogous Mukaiyama-Michael addition of various silyoxyfurans to enones, which proceeds through the classical iminium catalysis, will be presented. Also vinylogous Mannich reaction of a highly regio- and diastereo- selective TMSOTf promoted synthesis of chiral quaternary 3-aminooxindole butenolides from 2-silyloxy furans and chiral ketimines will be discussed.[4] This method provides a facile access to sterically challenging 3-aminooxindole butenolides having two quaternary centers in continuation in a very efficient way.

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INVITED LECTURE

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INVITED LECTURE

Enhanced Oxygen Evolution from Photosystem II Coupled to Chemically Modified Graphene

Graphene oxide (GO) is an atomically thin nanosheet that is derived from the chemical exfoliation of graphite. The availability of oxygen functional groups on GO makes it a versatile bidimensional substrate for self-assembly of proteins giving rise to hybrid bio-conjugates via both hydrophobic and functional group interactions. In this study we report the orientation specific self-assembly of photosystem II core complexes (PSII) on GO nanosheets that have been chemically modified with Ni^{2+} nitriloacetic acid coordination sites (GO-NiNTA), resulting in GO-NiNTA-PSII bio-conjugates in suspension.[1] Using chlorophyll fluorescence kinetic studies we demonstrate that PSII linked to the GO-NiNTA resin exhibits a quantum yield of photochemistry as high as 0.74, which is slightly lower than native PSII in aqueous buffer at pH = 6.5. The resin has the capability of partially preserving the activity of PSII for a limited number of turnovers in the absence of redox mediators, suggesting the possibility of direct electron transfer from PSII to GO. Oxygen evolution measurements indicate that immobilized PSII display twice the flash-induced oxygen yield of free PSII and an initial rate > 7900 mmol O_2 / (mg Chl · h) under continuous illumination using ferricyanide as terminal electron acceptor. This unprecedented initial rate corresponds to an oxygen turnover time of 14 ms per PSII and a remarkable initial volumetric photocurrent density of 5.5 mA/mL. Our work shows that GO-NiNTA are biocompatible substrates for the functional assemblies of natural photosynthetic components and provide valuable structural elements for the design of bio-inspired and bio-hybrid electron transport chains.

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Exploration of New Scaffolds as Promising Anti-Inflammatory and Anticancer Agents

Natural products gaining importance in modern drug discovery research due to ready available from variety of medicinal plants and novelty can be gained by modification or using synthetic approach which presumes fewer side effects. With this effort variety of scaffolds were synthesized and evaluated for their anti-inflammatory activity against TNF-α and IL-6 as well as anticancer activity using variety of cell lines from different cancer genesis. Based on the screening results, promising candidates will be discussed for their antiproliferative action in Panc1 (pancreas), H640 (non small cell lung carcinoma), Siha (cervix), ACHN (renal) and Calu-1 (lung) cancer cell lines and anti-inflammatory action in TNF- α and IL-6 inhibition with IC_{50} range between 0.1 to 5.1 µM and 0.08 to 0.5 µM respectively.

INVITED LECTURE

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Indole-Based Heterocycles as Novel Inhibitors of Tubulin Polymerization

A large number of indole-based heterocycles isolated from different microorganisms are reported to exhibit interesting biological properties.[1] Among the important heterocycles, many of the natural and synthetic indole-based heterocycles with diverse mechanism of action have been reported as lead anticancer molecules. Particularly, compounds consists of indole linked five-membered heterocyclic scaffold are known for their anticancer activities. For example, Labradorins (isolated from *pseudomonas syringae pv. Coronafaciens*) are known to exhibit significant inhibitory activity against various human cancer cells.[2] Natural bis(indole)alkaloids such as topsentin and nortopsentins demonstrated significant *in vitro* cytotoxicity against P388 cells. A number of indole-based anticancer agents are known to interact with microtubules/tubulin dynamic equilibrium.[2] Microtubule plays a crucial role in the development and regulation of cell shape by involving in a range of pivotal cellular functions.[1] Dynamic equilibrium of tubulin-microtubule is one of the most successful targets to identify novel anticancer agents. The structurally diverse natural and synthetic analogues capable of modulating the polymerization of microtubules are of considerable interest in anticancer therapy. The microtubule targeting agents like vinorelbine, taxanes, colchicine, podophyllotoxin and combreastatin are known to induce cell death by affecting apoptosis. In continuation of our efforts to identify potent and selective anticancer agents, recently we have designed and synthesized a series of diverse indolyloxadiazoles, indolylthiadiazoles and bis(indoles)heterocycles and screened for their *in vitro* anticancer activity against a panel of cancer cell line.[3] Some of the potent indole-based heterocycles exhibited selective cytotoxicity against cancer cell lines by modulating the tubulin polymerization. Detailed synthesis and anticancer activity results of identified novel indolylheterocycles will be presented in the conference.

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INVITED LECTURE

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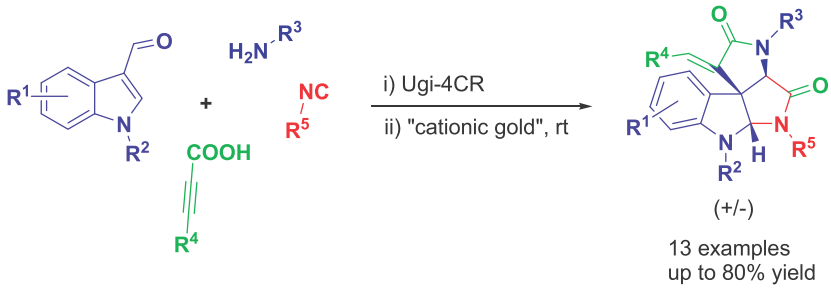
Cationic Gold-Catalyzed Heteroannulations

Gold catalysis is one of the fast growing research topics of modern organic chemistry. In this context, gold-catalyzed carbocyclization and heteroannulation strategies have recently attracted much attention due to the selective and efficient activation of the C-C triple bond towards a wide range of nucleophiles. Moreover, the combination of multicomponent reactions with gold catalysis, gives access to complex molecular architectures in few steps, as compared to traditional multistep processes. We will comment on our recent findings in this field. A concise route to indoloazocines[1] via a sequential Ugi/gold-catalyzed intramolecular hydroarylation[2] will be presented. A diversity-oriented approach to spiroindoles via a post-Ugi gold-catalyzed diastereoselective domino cyclization[3] will be described (Scheme), as well as a regioselective approach for the synthesis of pyrrolopyridinones and pyrroloazepinones employing a gold(I)/platinum(II) switch.[4]



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INVITED LECTURE

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Quest for New Antidotes against Toxicants

Chemical terrorism, or chemo-terrorism for short, doesn't get as much press as bio-terrorism, but the objectives are the same and the means even more readily available.

In both cases, the purpose is to intimidate or coerce governments or civilian populations, to further political or social objectives. The difference is the method: chemo-terrorism means poisoning the air, water and food supply using chemicals such as caustic acids, arsine, benzene, cyanide, hydrofluoric acid, mustard/T, ricin, sarin, and others.

The use of the organophosphorus (OP) compounds as pesticides (e.g. parathion, malathion, chlorpyripos) is prohibited in most part of the world but still are in use in the developing countries, owing to their effectiveness and low cost. Unfortunately, some of these OP compounds were evolved as chemical warfare (CW) agents in the form of nerve agents (NA) such as sarin, soman, tabun and VX. With growing threats of terrorist activities, and also the most recent incidents in Syria one should not decline repeated use of these NAs on a mass scale in the future. Further, the decontamination and/or destruction of large stockpile of NAs envisage a serious threat to human health. Therefore, the development of effective medical treatment regimen of OP poisoning has attracted the attention of many researchers. This involves with the discovery and development of antidotes against chem-bio agents for timely treatment of affected personnel.

Defence Research & Development Establishment (DRDE) is working in the area of defence against Chemical and Biological Warfare (CBW) agents for the last three decades. The core competence of DRDE has been in the development of state of the art technologies and systems for detection, protection and decontamination of chemical and biological warfare agents. This sustained work helps to build up DRDE as a center of excellence in CBW defence and related issues. In this context, the present talk will give a brief overview on the development of new antidotes and protection studies against the toxicants.

INVITED LECTURE

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Enzyme Immobilized on Nanogels as Triggered Drug Delivery

Nanogels, crosslinked three dimensional hydrophilic networks of less than 200 nm, are potential candidates for drug delivery, biosensors, and as supports for enzyme immobilization. Present presentation is an attempt to evaluate the recent developments, including our own work, in the use of nanogels as support in enzyme immobilization. The property profile of the immobilized enzyme versus the enzymes is dependent both on the structure of nanogel and immobilization technique followed. Nanogels are biocompatible and due to the high surface area these bind large amount the drugs or enzymes. At present there is a fast progress in the work reported on the use of nanogels for these applications. In the present talk the focus will be on the synthesis of biocompatible nanogels as supports for enzymes those have therapeutic applications such as uricase, glucose oxidase or catalase, and to discuss their therapeutic potential and efficacy of drug delivery with the immobilized enzyme triggered release of drugs, especially, insulin.

INVITED LECTURE

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INVITED LECTURE

Fluorine Containing Compounds – A New Class of Anti-Infective Agents

A cursory inspection of the medicinal chemistry literature reveals two obvious themes in the structures of current drug candidates: the ubiquity of nitrogen heterocycles and the popularity of organofluorine moieties. Therefore, it seems natural that a combination of these two structures will offer rich possibilities in the future of drug development. Unique properties of fluorine-containing heterocycles are of considerable importance in organic and medicinal chemistry. The replacement of hydrogen by fluorine in organic molecules has often led to dramatic changes in their physicochemical and biological properties [1,2]. This has a drastic effect on the overall electronic distribution within the molecule thereby affecting dipole moments and the acidity, basicity or activity of neighboring groups; any of which can affect molecular interactions with receptors or other interacting molecules [3].

Currently more than one fifty fluorinated compounds are used as pharmaceuticals. Therefore, the synthesis of fluorinated molecules play an important role in drug discovery and many pharmaceuticals, a few well-known shining examples are 5-fluorouracil, gemcitabine and emtricitabine, ciprofloxacin, ofloxacin, or norfloxacin, fluconazole, linezolid and tesetaxel possessed fluorine atoms [4,5]. Moreover, fluorine containing heterocyclic scaffolds display quite a broad spectrum of biological activities such as antibacterial [6-8], anti HIV [9], antitumor [10], anti-infective [11], antimalarial [12] and anticonvulsant [13]. In this context, we have synthesized several novel hybrid bioactive motifs clubbed with two or more fluorine containing heterocycles such as pyrazole, quinoline, quinazolinone, thiazole, thiazolidinone, 1,3,4-oxadiazole, pyrimidine and pyridine and these compounds were screened for their antimicrobial activity on several bacterial and fungal strains.

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Biologically Active Metal Chelates with Special Emphasis on Hydroxytriazenes

Metal chelates have been of particular interest as bio active compounds eversince the development of metal based drugs.Transition metal complexes have further played a very vital role in this area. our research group has been working on metal based bio active compounds using hudroxytriazenes and similar compounds as ligands.Reasonably good biological activities including antibacterial,antifungal,anti inflammatory and other activities have been found in our compounds.The talk focuses on versatility of triazenic moiety for the development of interesting bio active compounds including their metal complexes.

INVITED LECTURE

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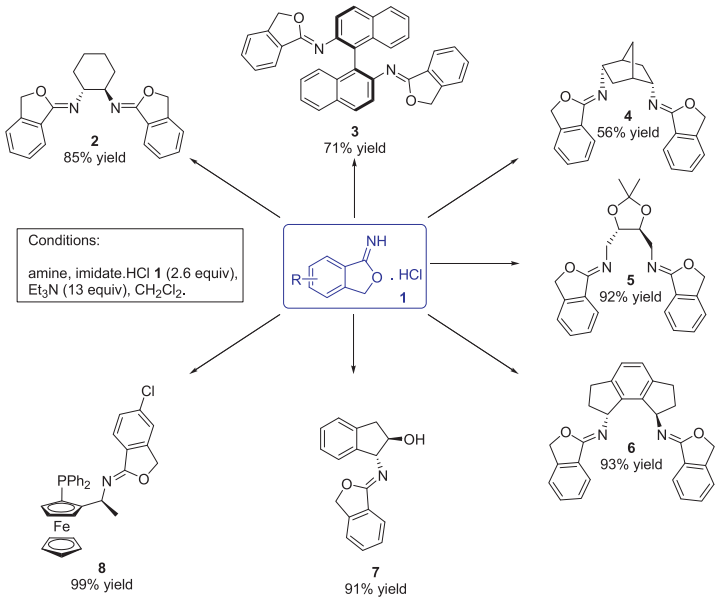
A Modular Approach to Chiral Imidates: A New Class of Nitrogen-Based Chiral Ligands as Tools for Medicinal Chemistry

Nitrogen-containing ligands are known as **cheap, readily accessible and stable** alternatives for phosphane ligands [1], which are often very sensitive to air and require a multistep synthesis [2]. We wish to present a **combinatorial approach** to **a novel type of nitrogen-based mono- and bidentate ligands** [3]. These ligands are characterized by their **modular structure**, allowing an **easy one-step synthesis** by simply combining two readily variable precursors which are either commercially available, or can be reached in only a few steps: a cyclic imidate **1** and a (chiral) amine, respectively diamine. These ligands show **promising results** in e.g. the Cu(I)-catalyzed asymmetric aziridination of methyl cinnamate, in asymmetric diethylzinc additions to benzaldehydes, in the Pd(0)-catalyzed asymmetric allylic alkylation and amination, and in Ir(I)-based asymmetric hydrogenation of alkenes, and hence are **promising tools for medicinal chemistry.**



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INVITED LECTURE

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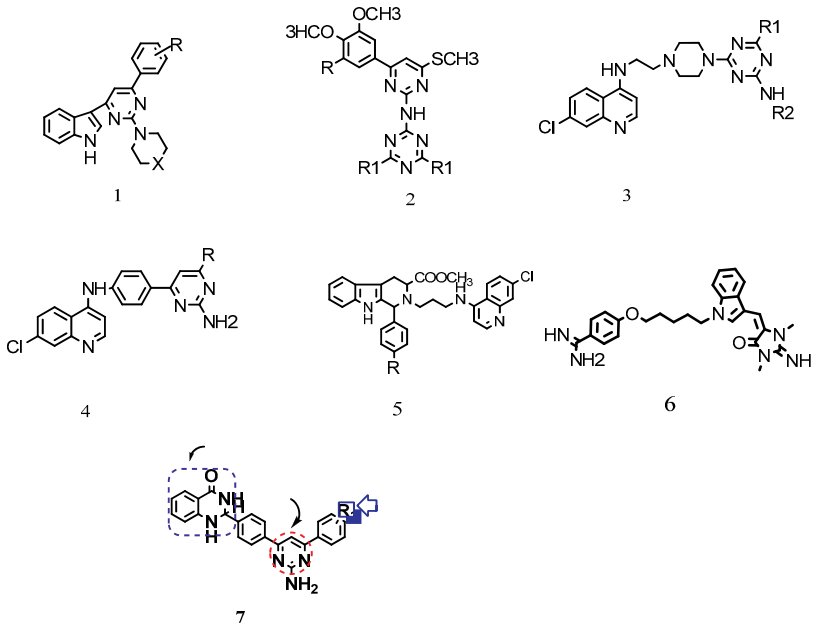
INVITED LECTURE

Synthesis of Bioactive Hybrid Molecules as Novel Therapeutic Agents

Drug research one of the important area of science. It is also very time taking and require multidisciplinary efforts. Nitrogen heterocycles are constituted a major class of existing drugs. Nitrogen heterocycles are widely distributed in nature and are essential to life process.They also play a vital role in the controlling the metabolism of all living cells. The activity of these molecules is attributed to their ability to interfere against several imortant biological target sites.

Keeping in view importance of natural products and nitrogen hetrocycles in antiparasitic area, we have synthesized novel heterocycles, natural product-heterocycles hybrid **1-5** as antiparasitic agents [1-10]. These hybrid molecules were synthesized by classical solution phase as well as on solid support. Several synthesized compounds have shown promising *in vitro* and *in vivo* antiparasitic activity against Malaria and Leshimania parasites. The design, synthesis and antiparasitic activity of these novel therapeutic agents will be discussed.



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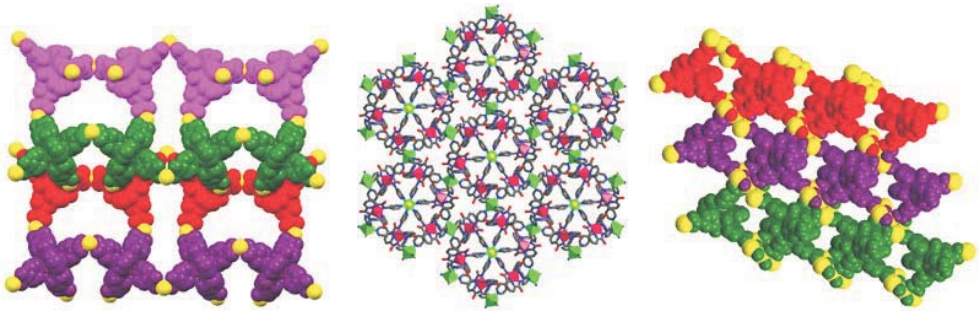
INVITED LECTURE

Organic Transformations by Designed Inorganic Catalysts

The designed networks are important catalytic materials as they offer well-defined pores and channels for substrate/reagent accessibility [1]. The ability to incorporate functional groups into porous networks makes them excellent candidates as the heterogeneous catalysts. Further, large surface area and porosity in such networks have the potential to endow them with the size- and shape-selective catalysis that is the hallmark of zeolites. The most remarkable features that heterogeneous catalysts offer are the easy recovery and reusability; and architecture dependent catalysis. Despite significant progress in heterogeneous catalysis, it remains a great challenge to engineer a strong Lewis acidic/basic site or redox-sensitive site in networks to expand applications towards many catalytic processes. Our synthetic strategy uses a transition metal ion to assemble simple ligands into a coordinated complex that can serve as the molecular building block [2-9]. These building blocks have been utilized for the syntheses of discrete heterobimetallic complexes [7-9] as well as two– (2D) or three–dimensional (3D) networks [2-6]. Notably, the judicious selection of Lewis acidic or redox-sensitive metals in such materials has been utilized by displaying heterogeneous catalysis including regio-selective, stereo-selective, chemo-selective and size-selective reactions [2-10]. The present talk will discuss the development of molecular building blocks for the generation of designed architectures and their application in catalysis.



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Bacterial Sec A as a Target for the Development of Antimicrobial Agents

The rapid emergence of bacterial drug resistance is presenting an alarming public health issue worldwide. Thus any effort to develop new antimicrobial agents should be focused on this key issue. Along this line, SecA is an essential protein translocase responsible for protein secretion or integration into membrane. SecA inhibition leads to bacteriostatic and bactericidal effects as well as reduced secretion of virulence factors. Furthermore, because SecA is a membrane protein, it is accessible from the extracellular matrix. Thus, efflux pumps, which are responsible for multi-drug resistance, have little negative effect on the potency of SecA inhibitors. For all these reasons, SecA is emerging as an excellent target for developing broad-spectrum antimicrobial agents with a novel mechanism of action. This lecture will discuss the nature, and structure and function of SecA as well as known SecA inhibitors.

INVITED LECTURE

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Studies on Herbal Medicament, A New Anti-Stroke Agent

Curcuma longa (C. longa), a perennial herb, is a member of the *Zingiberaceae* (ginger) family and possesses a wide array of biological activity. CSIR-CDRI had developed Herbal medicament (HM), a standardized hexane soluble extract of *Curcuma longa* rhizomes, as a new anti-stroke agent. Separation of marker compounds, validated HPLC analysis method of estimation of these compounds in different batches of HM oil and capsules, stability studies as per ICH guide lines including stability testing, forced degradation studies of ar-turmerone in pure form, bulk HM oil and HM capsule formulation will be discussed.

INVITED LECTURE

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INVITED LECTURE

Natural Product Framework Synthesis: Expeditious Concise Synthesis of Dibenzo[B,D]Oxepines, Dibenzo[B,D]Thiepines and Benzo[B]Pyrano[2,3-D]Oxepines through C-C Insertion and Ring Transformation Reactions

Dibenzoxepine framework is commonly present as substructure in numerous **natural products.** Cularinoids, a group of sixty isoquinoline alkaloids are characterized by the presence of dibenzoxepine skleton. The oxidized cularinoids are known to display significant cytotoxic activity and have been extensively used in treatment of anxiety, depression and schizophrenic psychoses.[1-4]Marked pharmacological activity of 1-Benzoxepines[5] had earlier prompted us to synthesize 5-substituted and 4,5-disubstituted-1-benzoxepines as α-sympathomimetic and potential hypotensive agents.[6-8] A novel concise synthesis of dibenzo[b,d]oxepines, Dibenzo[b,d]thiepines and Benzo[b]pyrano[2,3-d]oxepines has been developed involving C-C insertion and ring transformation reactions.

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Exploring Heme as a Target for Antimalarials

Malaria remains a major health problem in much of the tropical world. Despite decades of use, the biological targets of most of the current clinical antimalarials remain incompletely understood. A case in point is the quinoline class of compound. These have been thought to inhibit heme detoxification in the malaria parasite, but we have only recently demonstrated that the archetype of this class, chloroquine, causes a dose dependent increase in free heme in the parasite, which is probably responsible for parasite death. Despite widespread chloroquine resistance, the target remains potentially viable, because resistance is not directly associated with the heme detoxification mechanism. We have therefore concentrated considerable effort on both attempts at rational design of new heme targeting antimalarials and at high throughput screening efforts. These will be discussed.

INVITED LECTURE

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DMA a Bisbenzimidazole: An Odyssey of a Small Molecule as Radioprotectant

Ionizing radiation causes radiolysis of cellular water, generating reactive oxygen species (ROS), causing DNA damage. Radioprotectors protect the normal cells from the unwanted radiation damage. Since the beginning of the nuclear era, despite extensive research on the development of radioprotectors from natural and synthetic compounds, success has been limited. The only clinically acceptable radioprotector, amifostine, has inherent dose-limiting toxicities and has therefore stimulated extensive search for nontoxic, effective, and alternative radioprotectors. We have developed a cytoprotective radioprotector DMA, having a bisbenzimidazole nucleus. Relative quantitation of gene expression of the identified proteins and their interacting partners led to the identification of MAP3K14 (NFkB inducing kinase) as one of the plausible target. Subsequently, over expression and knock down of MAP3K14 suggested that DMA affects NFkB inducing kinase mediated phosphorylation of IKKα and IKKb both alone and in the presence of ionizing radiation. Our results demonstrated 3.62 fold increase in NFkB activation in DMA treated cells as compared to control cells. This activation was further increased by 5.8 fold in drug + radiation (50μM + 8.5 Gy) treated cells in comparison to control. We observed 51% radioprotection in untreated cells that attenuated to 17% in siRNA NIK treated U87 cells at 24h. In addition we studied the effects of DMA on the radiation and transcriptional response of HEK293 cell lines also. Our results, suggested that the treatment of DMA increased the level of phosphorylated AKT in HEK cells in presence of radiation, and this was consistent with the alteration of DNA-PKcs. Pharmacokinetic (PK) evaluations and bioavailability measurements proved superior in vivo efficacy, higher AUCs, greater residence time of DMA.

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INVITED LECTURE

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Cytotoxic Coscinamide Analogues Inhibit Tubulin Polymerization and Cause cell Death via Apoptosis

Cancer is a collection of diseases hallmarked by uncontrolled cell division. Cancer treatment involves varying combinations of surgery, radiation, chemotherapy and hormone therapy. Chemotherapy employs the use of drugs that kill the rapidly dividing cells (characteristic of cancer cells). Various chemotherapeutic drugs such as paclitaxel and vinblastine interrupt cell division by binding to tubulin (a protein responsible for spindle formation, a critical step in cell division). For more than 50 years, tubulin binding drugs have been used to treat cancer, Scientists are still in search of novel anti-cancer compounds targeting tubulin for two reasons; (1) patients develop resistance to existing drugs and (2) tubulin is one of the most validated targets for cancer treatment. A series of eighteen synthetic coscinamide analogues were evaluated for their cytotoxic effects on 5 different cancer cell lines. Our initial screen using MTT cell proliferation assay identified three compounds that caused cell death with IC_{50} less than 0.5 μM. Preliminary mechanism of action studies indicated that these compounds induced a caspase-dependent apoptotic response and exert their anticancer activity through inhibition of tubulin polymerization (IC_{50} = 20 nM).

INVITED LECTURE

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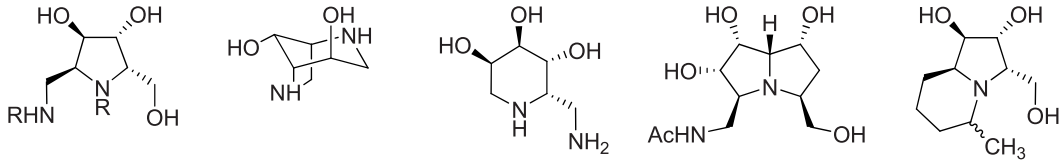
INVITED LECTURE

Natural products to Natural Products and their Mimics

Total syntheses of natural products of biological and medicinal importance and their mimics continue to be in the forefront of organic research since last few decades. Together with chemical biology and drug discovery, organic syntheses provide an ideal combination to acquire fundamental knowledge of life sciences thereby providing excellent opportunities to understand the complex biological functions and accordingly develop drugs for human well-being. Over the years, carbohydrates have been recognized as naturally occurring compounds endowed with a wealth of stereochemical attributes and have been used as chiral starting materials in the total synthesis of a wide range of natural products. Further, the diverse structural features of carbohydrates and their involvement in various recognition processes offer substantial scope in gaining more knowledge of glycobiology and diseases at molecular level, that may eventually lead to the development of carbohydrate based drugs. In the last few years, we have accomplished the synthesis of a number of natural products and their mimics, from readily available and natural carbohydrates, through a diversity-oriented approach, involving some novel transformations.[1–8] Our recent research work on the synthesis of the following compounds and their glycosidase inhibitory activities will be presented.



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DNA Structural Polymorphism: A Biologically Relevant Phenomenon

Conformational flexibility of DNA is central to its biological functions. Information on the secondary structures and conformational manifestations of eukaryotic DNA and their biological significance with reference to gene regulation and expression is still limited. A major concern and focus of today's scientific community is to understand the protein/receptor dysfunctioning which contributes to the disease etiology. This understanding largely aims to investigate the influence of Single nucleotide polymorphisms (SNPs) on protein/ receptor functioning. Naturally occurring mutations and various SNP sites may stabilize or destabilize the local secondary structures, affecting the gene expression by a change in the protein–DNA recognition patterns. In one way or other, SNPs can cause structural changes at various levels of DNA, RNA and Protein. Structural polymorphisms and geometrical switching of DNA exhibited by SNP may cause variations in palindromic or quasi-palindromic segments within the regulatory locus control region (LCR) of human b-globin gene.

I will discuss here in brief few examples, showing how the sequence at SNP sites, in various solution conditions dictate the generation of DNA structures. It is proposed that groups of such structural motifs might act as regulatory elements in various gene expressions.

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INVITED LECTURE

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Plasmodium Falciparum Purine Nucleoside Phosphorylase (PfPNP): A Potent Drug Target

The malaria parasite obtains preformed purines by the salvage pathway. The purine salvage pathway in *Plasmodium* is streamlined with adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP) and hypoxanthine-xanthine-guanine-phosphoribosyltransferase (HGPRT) representing the major pathway for purine acquisition. The enzyme purine nucleoside phosphorylase (PNP) catalyzes the phosphorolysis of inosine to ribose-1-phosphate and hypoxanthine, which is the primary purine precursor for the salvage pathway.

Plasmodium falciparum Purine nucleoside phosphorylase (PfPNP) was successfully cloned and expressed in BL21 (DE3) E.Coli host cell. Protein was purified by affinity chromatography. PfPNP a homohexamer contained single tryptophan residue per subunit, the role of this tryptophan residue in catalysis was studied that accepts inosine and guanosine but not adenosine for its activity. The enzyme shows disorder to order transition during catalysis.Modification of tryptophan residue by N-bromosuccinamide resulted in complete loss of activity showing its importance in catalysis. Inosine was not able to protect enzyme against N-bromosuccinamide modification. Extrinsic fluorescence studies revealed that tryptophan might not be involved in substrate binding.Results of studies indicated that tryptophan residue is essential for catalysis and not required for substrate binding.

Biochemical and biophysical properties of PfPNP enzymes were studied in dilute buffer system, which are far from the crowded physiological condition of cell. The enzyme kinetics and refolding of (PfPNP) under crowded conditions showed that enzyme catalytic efficiency was inversely affected in the presence of polyethylene glycols and Dextran whereas it was increased in the presence of osmolytes.The knowledge about modulation of inherent properties of this enzyme in crowded environment will be helpful in better understanding of this drug-target enzyme and in further inhibitor design.

INVITED LECTURE

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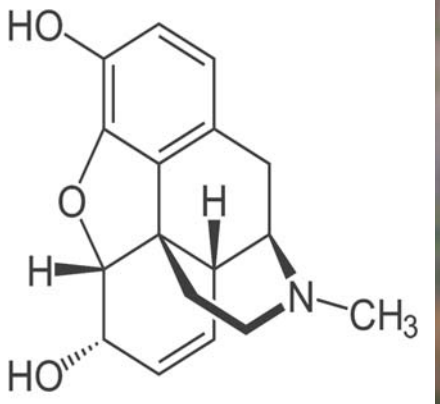
BUCHI Solutions for Regulated Pharmaceutical Industries

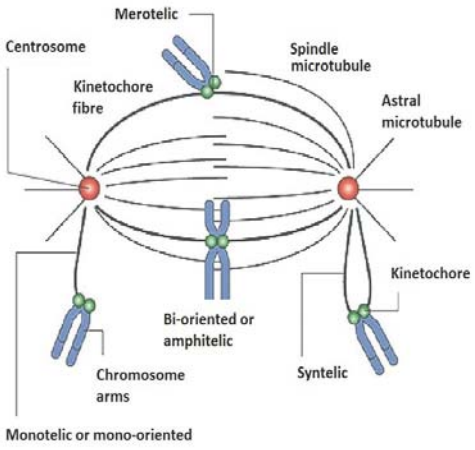
Drug discovery and development for pharmaceutical industries require safe, efficient and compliant sample preparations and analytics. BUCHI offers various solution for making your research and Development, quality Control or production/ Manufacturing more efficient.

INVITED LECTURE

ISCBC - 2014

Short Lecture





20th ISCB International Conference

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SHORT LECTURE

Organocatalytic Cascade Strategy for Synthesis of Small Molecule Natural Products (SMNPs)

Organocatalysis has grown-up rapidly and applied successfully to several different enantioselective reactions in last one decade and therefore, now considered as the "*third pillar*" of enantioselective catalysis, together with biocatalysis and metal catalysis.[1] Additionally, Small molecule natural products (SMNPs) continue to inspire the development of new therapeutic agents for the treatment of a plethora of diseases that confront humankind in an age where the rapid emergence of multi-drug resistant forms of these are becoming an increasing threat. In the continuation of our interests,[2] recently we have developed new [3+2] and [4+2] annulation methods for the synthesis of heterocyclic SMNPs through the organocatalytic *in situ* generation of 1,3- and 1,4-carbon dipole.

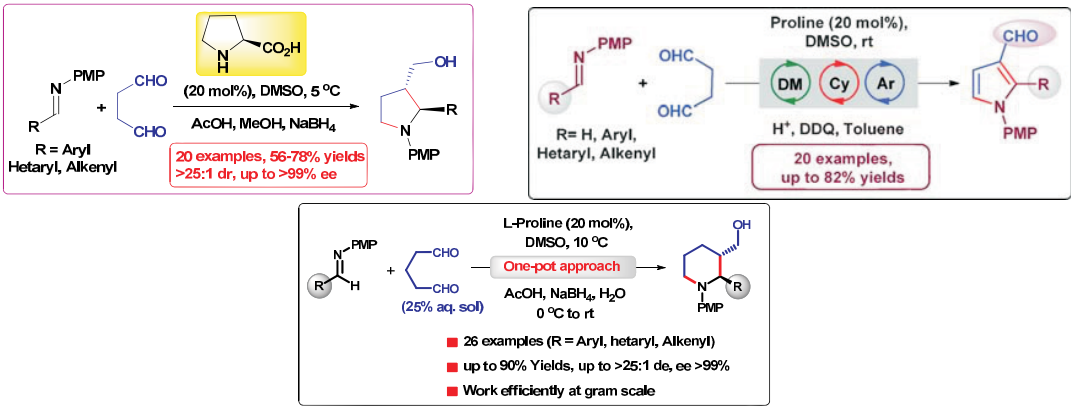

Figure 1: 1,3-and 1,4-carbon D-A annulation approaches for the synthesis of SMNPs

In-situ generation of amine catalyzed 'enamine' from easily available molecule *i.e.* succinaldehyde and glutaraldehyde, act as 1,3- and 1,4-carbon dipole (*donor-acceptor* mechanism). The present 1,3-carbon dipolar annulation concept is very compatible and even more greener as compare to the only two methods known earlier and further application in [3+2] annulation of aldimines to synthesize substituted pyrrolidines (Figure 1).[3] Additionally, the first organocatalytic asymmetric synthesis of substituted piperidines have been developed in our group through 1,4-carbon D-A strategy. [2d] This strategy was further extended to the first direct synthesis of pyrrole-3-carboxaldehyde as an alternative to Paal-Knorr method for pyrrole synthesis from 1,4-dicarbonyl compound (succinaldehyde) using direct Mannich-cyclization-aromatization sequence.[2c] Details of the D-A concept, design and synthetic strategy for further application in synthesis of SMNPs will be presented here.

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Structural Analysis and Functionalization of Polysaccharides

Polysaccharide based drugs and vaccines have revolutionized the modern therapy. Recent investigations on polysaccharides have signified their fundamental role in normal cell functions as well as in major disease pathologies including cancer, cardiovascular and inflammatory diseases. Several vaccines based on the purified cell wall polysaccharide (CPS) or neoglycoconjugates are now either commercially available or under development, the list includes, vaccine against *Neisseria meningitidis, Streptococcus pneumonia, Haemophilus influenza* type 2 (Hib), *Shigella flexineri, Salmonella typhi, Vibrio cholera*, to name a few. Besides this, intense research efforts are being made for development of vaccine for Malaria, Leishmeniasis, Cancer, HIV, Pneumonia, Influenza, Anthrax, etc. Current researches on natural polysaccharides have revealed much greater role of natural polysaccharides in biological systems than ever imagined. The examples include lentian, acarbose, fucodians, glycosaminoglycans, galactomannans, xyloglucans etc.

Exploration of the traditional knowledge in finding sources worthy of study has led to novel and hitherto unexplored chemotherapeutic plant polysaccharides. The first part of the study details the isolation, purification, gel permeation and paper chromatographic analysis, isolation of oligosaccharides, methylation studies as well as gas-liquid chromatographic analysis of the oligosaccharides and polysaccharide and finally spectroscopic analysis with a view to establish the structure of interesting bioactive plant polysaccharides viz. *Cassia tora* seed, *Dalbergia sissoo leaves, Tinospora cordifolia* stem. Enthused by the bioactivity of polysaccharides, it has also been embarked to study the fine polysaccharide structure of *Vitex negundo*, *Hippophae salicifolia*, *Malvastrum coromandelianum* and the medicinal potential of the purified bioactive polysaccharides and fractions thereof.

The latter part discusses simpler and efficient routes towards chemical modification of hyaluronic acid due to its remarkable physico-chemical characteristics especially its visco-elasticity, ability to bind and retain water and its unique biological functions. Hyaluronic acid thus plays an important role in tissue hydration, lubrication and cellular function and as a mechanical support for the cells of many tissues, such as the skin, tendons, muscles and cartilage. HA is employed in a wide range of current and developing applications within cosmetics, ophthalmology, rheumatology, drug and gene delivery, wound healing and tissue engineering. The paper discusses important modifications done on hyaluronic acid using novel eco-friendly and cost effective routes and their applications in different biomedical applications.

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SHORT LECTURE

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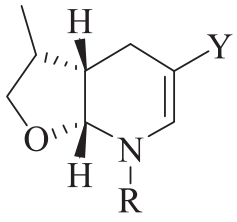
SHORT LECTURE

New Methodology for the Synthesis of Bicyclic Heterocyclic Systems from 1,4-Dihydropyridines

Continuing our research on the development of new transformations of 1,4-dihydropyridines **(1)**, we have recently described some 'non-biomimetic' oxidations of these compounds, in which the normal production of the corresponding pyridinium salt is avoided[1]. The methodology represents a new synthetic entry to a wide range of functionalized tetrahydropyridines (**2**) stereoselectively as potential precursors of bioactive or natural products such as azasugars. This methodology also affords bicyclic heterocyclic systems [2,3] of biological importance. Electrophilic interaction of halogen with *N*-alkyl-1,4-dihydropyridines followed by the reaction of iminium salt with nucleophile unsaturated alcohols, stereoselectively lead to the functionalized tetrahydropyridines which are converted into corresponding hexahydrofuro[2,3-b]pyridine derivatives **(3)** in satisfactory yields by free radical cyclisation reaction.



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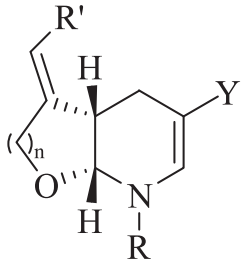

n = 1,2 **3**

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Lead Molecules from the Indian Medicinal Plants for Metabolic and Infectious Diseases

Written records of the use of natural products as medicinal agents date back thousands of years. The oldest records come from Mesopotamia and date from about 2600 BC, however, it was not until the early 1800's that the active principles from plants were isolated. Natural products isolated from plants, animals and microorganisms have made an important impact on curing the dreadful diseases for example taxol, vinca alkaloids, podophyllotoxins camptothecin derivatives for cancer treatment; pencillins, streptomycins, tetracyclines as antibiotics; quinine and artemisinin for malaria treatment.

In continuation of drug discovery program on the Indian Medicinal Plants at our institute we identified several lead molecules for various diseases such as diabetes, dyslipidemia, malaria, leishmania, cancer etc. through activity guided extraction, fraction and isolation work. From *Aegle marmelos*[1] and *Trigonella foenum graecum*[2] we identified an alkaloidal amide (aegeline) and an unusual amino acid (4-hydroxyisoelucine) respectively, which exhibits *invivo* antihyperglycemic activity and lipid lowering activity. *Ficus racemosa*,[3] a well known Indian medicinal plant provided us a triterpne (α-amyrin acetate), which shows antihyperglycemic activity in streptozotocin induced diabetic rats. Several derivatives of the active principle (amyrin) have been prepared, which have better therapeutic value. *Aegle marmelos* also provided a triterpene (lupeol), which shows lipid lowering activity in hamster model.[4] Few derivatives of the active constituents (lupeol) were prepared to improve the activity of the compound. Modified furanoflavonoid (semiglabrin and pesudosemiglabrin) isolated from *Indigofera tinctoria*[5] exhibits potent lipid lowering activity. We also identified prenylated chalcones[6] such as medicagenin, muchiwarin from *Crotalaria medicagenia* as antimalarial agents. Chromenodihydrochalcones isolated from the *C.ramosissima*[7] exhibits antileishmanial activity. On the basis of this natural products leads several analogues of active principles prepared. Some of the synthetic chromenochalcones exhibits potent antileishmanial activity and antimalarial activity.[8] We also identified an alkaloid (peganine) from the seeds of *Peganum harmala*,[9] which exhibits *invivo* antileishmanila activity. Larger quantities of 2-deacetoxytaxinine J was isolated from the bark of *Taxus baccata* (ssp. *wallichiana*)[10] which is related to taxol and prepared several derivatives to develop potent anticancer agent. Recent developments in the natural products drug discovery including our results will be discussed.

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SHORT LECTURE