Medicinal Chemistry Conference

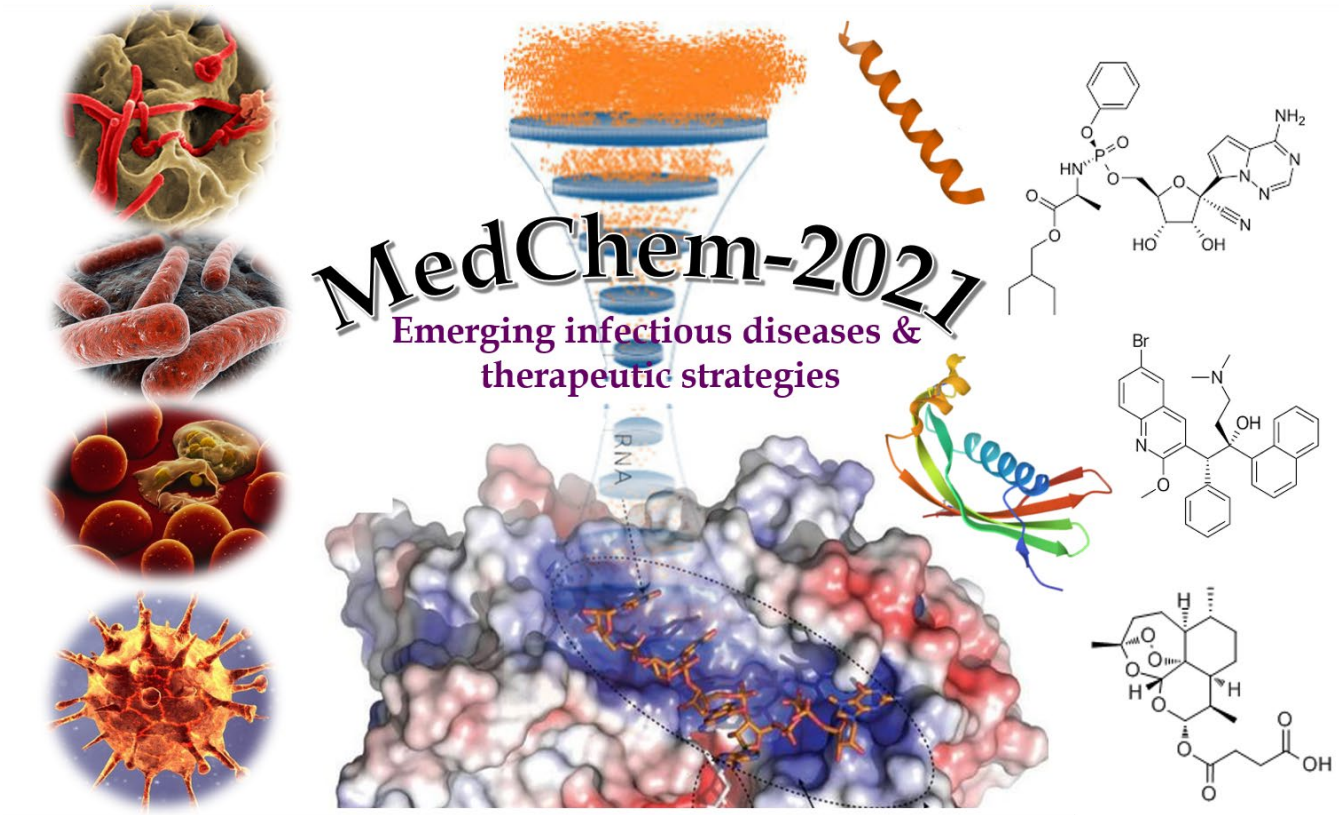
(MedChem-2021)

on

Emerging infectious diseases and therapeutic strategies

December 01-03, 2021

Organized as part of the activity of AstraZeneca Endowment for Education and Research in Medicinal Chemistry



Department of Chemistry
Indian Institute of Technology Madras, Chennai

Medicinal Chemistry Conference
(MedChem 2021)

Abstracts

Indian Institute of Technology Madras, Chennai

December 01-03, 2021

Message from the conveners

On behalf of the department of chemistry IIT Madras, it is our pleasure to warmly welcome you to MedChem-2021 conference which will focus on the topic 'Emerging infectious diseases and therapeutic strategies'. We have been conducting such theme-based biennial conferences since 2009, and is part of our continuing efforts to promote education and research in the area of Medicinal Chemistry through IITM-AstraZeneca endowment program. Considering the ongoing pandemic, this is being conducted in an online mode.

We are fortunate to have ninteen eminent speakers with expertise in different areas related to the theme of this conference. They include renowned physicians, biologists, medicinal- and synthetic chemists. We believe that the theme chosen for this event is very timely, and this will be a good platform for people from different areas of expertise to share their knowledge. We also hope that this will motivate students to take-up challenging problems in the area of chemistry-biology interface for the benefit of society at large

In addition to talks from from experts, we have included 'mini oral presentations' by research scholars from different institutes across the country. This is a substitute for poster session and hopefully will be more effective in an online platform. We are sure that all the lectures and mini oral presentations will be enlightening, and this event will add three memorable days to our research life.

Dr. Muraleedharan K. M.

Dr. Hema Chandra Kotamarthi

Patron

Professor Bhaskar Ramamurthi, Director, IIT Madras

Chairperson

Professor Sanjay Kumar, Head, Chemistry department

Conveners

Dr. K. M. Muraleedharan

Dr. Hema Chandra Kotamarthi

Student Volunteers: Pushpkant Sahu, K.V.Akshaya, Deep Kumar Barman, P.P.Archana, Jais K.

Scientific Advisory committee

Prof. Indrapal Singh Aidhen	Dept. of Chemistry, IITM, Chennai
Prof. S. Sankararaman	Dept. of Chemistry, IITM, Chennai
Prof. Guhan Jayaraman	Dept. of Biotechnology, IITM, Chennai
Dr. Srinivas Reddy	Director, IIIM, Jammu.
Dr. Srivari Chandrasekhar	Director, IICT Hyderabad
Dr. Ram Vishwakarma	Scientific Advisor, CSIR

Programme

MedChem 2021: Programme schedule

Day 1, Wednesday, December 1st, 2021

09:00 – 09:20	Inaugural function Welcome address HoD's address Director's address Vote of Thanks
	SESSION I (Chair: Prof. S. Sankararaman)
09:20 – 10:20	Keynote Lecture – **Prof. Randeep Guleria,** *Director, AIIMS-New Delhi.* *TBA (To be announced)*
10:20 – 10:30	**Break**
	SESSION II (Chair: Prof. Archita Patnaik)
10:30- 11:05	Invited Lecture 1 - **Dr. Siddharth Chopra** *CDRI, Lucknow* ***"Drugs for bad bugs: Progress amongst challenges"***
11:05- 11:40	Invited Lecture 2 - **Dr. Ishu Saraogi** *IISER, Bhopal* ***"A Chemical Approach for the Development of Novel Antibacterial Agents"***
11:40 – 11:45	Break
	SESSION III (Chair: Prof. Mangala Sunder)
11:45 – 12:20	Invited Lecture 3 – **Prof. Rupinder Kaur,** *CDFD, Hyderabad.* ***"Glycosylphosphatidylinositol-linked aspartyl proteases: Multifunctional enzymes and key mediators of Candida glabrata-host interaction"***
12:20-12:50	Mini Oral presentations
14:30- 14:50	Mini Oral Presentations

SESSION IV (Chair: Prof. R Krishna Kumar)

15:00 –16:00	Plenary Lecture 1 – **Prof. Raghavan Varadarajan,** *Indian Institute of Science, Bengaluru.* ***"Immunogen design for COVID-19 and influenza"***
16:00 –16:35	Invited Lecture 4– **Dr. Ravichandran Rajan** *MIOT International, Chennai.* ***"Use of indomethacin in Covid 19 patients"***
16:35 – 16:45	**Break**

SESSION V (Chair: Prof. Sanjay Kumar)

16:45 –17:20	Invited Lecture 5– **Dr. Anoop Kumar,** *BM Hospitals, Kozhikode* *TBA*
17:20 – 17:50	Mini Oral Presentations
17:50 - 18:00	Day's Summary
18:00 – 18:30	Mini Oral Presentations

Day 2, Thursday, December 2nd, 2021

SESSION VI (Chair: Prof. Guhan Jayaraman)

09:00 – 10:00 Plenary Lecture 2 – **Prof. Arnab Chatterjee,**
California Institute for Biomedical Research (Calibr), La Jolla, USA

"Drug Repurposing and Optimization of Oral Drug Combinations to Treat and Prevent CoV-2 Infections"

10:00 – 11:00 Plenary Lecture 3– **Dr. Paul Ramesh**
Apollo Hospitals, Chennai

"The physiological basis of clinical manifestations of systemic inflammatory (SIRS) and sepsis syndromes."

11:00 – 11:10 **Break**

SESSION VII (Chair: Prof. Dillip Kumar Chand)

11:10 – 11:45 Invited Lecture 6 - **Dr. Manidipa Banerjee,**
IIT Delhi, New Delhi.

"The role of viral membrane proteins in enveloped virus budding and development of antivirals"

11:45 – 12:20 Invited Lecture 7 - **Dr. Jayanta Haldar**
JNCASR, Bengaluru

"Outwitting antibiotic resistance: A perpetual battle"

12:20 - 12:50 Mini Oral presentations

14:30- 14:50 Mini Oral Presentations

SESSION VIII (Chair: Prof. Indrapal Singh Aidhen)

15:00 –16:00 Plenary Lecture 4 – **Prof. Mark Bronstup,**
Helmholtz centre for infectious diseases, Germany.

"Assault, Siege or Trojan Horse Strategy: Use of Natural Products to Fight Bacterial Infections"

16:00 –16:35 Invited Lecture 8- **Dr. Kirandeep Kaur Samby**
Medicines for Malaria Venture, Switzerland.

"***Opening up anti-malarial Drug Discovery"***

16:35 – 16:45 **Break**

SESSION IX (Chair: Prof. N N Murthy)

16:45 –17:20	Invited Lecture 9 – **Dr. Vani Janikiraman,** *IIT Madras, Chennai.* ***"Mycobacteria's smart arsenals: Role of Small Intermediary metabolites (SIMs)"***
17:20 - 17: 55	Invited Lecture 10– **Dr. Niti Kumar,** *CDRI, Lucknow.* ***"Probing into genome and proteome maintenance pathways in the human malaria parasite for design of alternative intervention strategies."***
17:55 – 18:25	Mini Oral presentations
18:25 - 18:35	Day's Summary
18:35 – 19:00	Mini Oral presentations

Day 3, Friday, December 3rd, 2021

SESSION X (Chair: Prof. G. Sekhar)

09:00 – 10:00	Plenary Lecture 5 – **Prof. Jason Sello,** *School of Pharmacy, UCSF, USA* ***"Illuminating New Pathways in Biology and Anti-Bacterial Drug Development Using Small Molecules"***
10:00 – 11:00	Plenary Lecture 6 – **Prof. Srinivas Hotha,** *IISER Pune, Pune.* ***"Diversity to Discovery – A Serendipitous 'Golden' Entry into Glycochemistry"***
11:00 – 11:10	**Break**

SESSION XI (Chair: Prof. M. V. Sangaranarayanan)

11:10 – 11:45	Invited Lecture 11 - **Prof. Sanjib Senapati,** *IIT Madras, Chennai.* ***"Identifying crucial E-protein residues responsible for unusual stability of Zika virus envelope"***
11:45 – 12:20	Invited Lecture 12 – **Dr. Arindam Talukdar,** *IICB, Kolkata.* ***"Target repurposing for a new virus: Tinkering endosomal Toll-like receptors"***
12:20- 12:30	Day's Summary
12:30 -12:45	Concluding remarks

Plenary Lecture (PL)

PL-1

Immunogen design for COVID-19 and influenza

Prof. Raghavan Varadarajan

Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560012, India

As is clear from the ongoing pandemic, respiratory viruses are clearly one of the biggest human global health threats. Current COVID-19 vaccines have shown varying degrees of efficacy in different geographic locations and there are concerns about how recent viral mutations might impact vaccine efficacy. Neutralizing antibodies that prevent viral entry into host cells are currently the clearest correlate of protection and are largely directed against the Receptor Binding Domain of the viral Spike protein. Most current vaccine formulations require low temperature storage, a major impediment to widespread deployment. We have developed highly expressed, thermotolerant, and stabilized Receptor Binding Protein derivatives that in small animals elicit antibodies that neutralize all current Variants of Concern and protect hamsters and transgenic mice from high dose pathogenic viral challenge. Such subunit vaccine formulations hold great potential to combat COVID-19 and are currently in clinical development [1,2] with trials planned in the coming year. Influenza is another respiratory virus that can cause tens of millions of deaths during a pandemic. There are good vaccines against seasonal influenza but these need to be updated annually because of rapid viral evolution. These vaccines elicit antibodies against variable regions of hemagglutinin (HA), the major surface protein of influenza virus. We have developed various novel immunogen designs to elicit broadly protective antibodies against influenza, some of which are in clinical development.

1. Design of a highly thermotolerant, immunogenic SARS-CoV-2 spike fragment immunogen Malladi et al, (2020) *Journal of Biological Chemistry*. 2020 doi: 10.1074/jbc.RA120.016284

2. Immunogenicity and protective efficacy of a highly thermotolerant, trimeric SARS-CoV-2 receptor binding domain derivative Malladi et al, (2021) *ACS Inf Dis* 7:2546-2564

PL-2

Drug Repurposing and Optimization of Oral Drug Combinations to Treat and Prevent CoV-2 Infections

Prof. Arnab Chatterjee
California Institute for Biomedical Research (Calibr), La Jolla, USA

From the onset of the COVID-19 pandemic in late 2019, the need for determining safe and cheap oral small molecule drugs as anti-virals has been critical as an approach to reduce disease burden. We began known drug screening in variety of SARS-CoV-2 assays starting in January 2020 and establishing an in vitro and in vivo models (rodent disease models, primary cell cultures) to select best candidates for repurposing. In addition, we have embarked on medicinal chemistry optimization of polymerase and protease inhibitors that will be discussed.

PL-3

The physiological basis of clinical manifestations of systemic inflammatory (SIRS) and sepsis syndromes

Dr. Paul Ramesh, Apollo Hospitals, Chennai

SIRS and sepsis are among the commonest complications in the ICU with mortality ranging from 40-70%. A wide variety of agents both infective (bacterial, viral, fungal and parasitic) and non-infective are responsible. Both causes and treatment of various diseases can result in the syndrome. Accurate risk estimation is still not possible. A deeper understanding of the clinical manifestations of the syndrome based on altered physiology will help investigators frame research questions more accurately. The experience of post operative, non COVID and COVID - 19 patients of our unit is presented along with the underlying the patho- physiology. The aim of the presentation is to explain to basic science investigators clinical jargon and gaps in current knowledge to bridge the gap between bench and bedside.

PL-4

Assault, Siege or Trojan Horse Strategy: Use of Natural Products to Fight Bacterial Infections

Prof. Dr.Mark Brönstrup,

Helmholtz Centre for Infection Research, Braunschweig, Germany; Biomolecular Drug Research Centre (BMWZ), Hannover, Germany; German Centre of Infection Research, Site Hannover-Braunschweig, Germany

Multidrug resistant bacterial pathogens have become a major health concern. Especially infections by gram-negative bacteria are challenging, since their complex cell membrane architecture strongly impedes the uptake of drugs. Because microbial natural products continue to be the prime source to tackle these issues, we have investigated natural products as the basis for novel antibiotic.

The armeniaspirols represent a novel class of antibiotics with a unique spiro[4.4]non-8-ene chemical scaffold and potent activities against gram-positive pathogens.[1] I will report a concise total synthesis of (±) armeniaspirol A and disclose their mechanism of action, that might be also valid for other chloropyrrole-containing natural products.[1] A broad spectrum of gram-positive and gram-negative pathogens is addressed by cystobactamids, oligo-arylamids originally isolated from Cystobacter sp. Our efforts to optimize the antibiotic properties of the cystobactamids by medicinal chemistry will be presented.[2]

Beyond a classic 'assault' of bacteria with such antibiotics, the conjugation of natural products to targeting functions has been beneficial to improve their drug properties.[3] In the so-called Trojan Horse Strategy, antibiotics are conjugated to siderophores to hijack the bacterial siderophore transport system, and thereby enhance the intracellular accumulation of drugs.[4] We present novel artificial siderophores, characterize their transport and resistance mechanisms, and their efficacy when coupled to antibiotic natural products.[5] Finally, we present a novel approach for the selective bacterial targeting and infection-triggered release of antibiotic conjugates in the alternative siege concept, using the lipopeptide colistin as the antibiotic effector.[6]

References:

1) C. Dufour et al. *Chem. Eur. J.* **2012**, *18*, 16123-16128; N. Arisetti et al., unpublished. 2) G. Testolin et al., *Chem. Sci.* **2020**, *11*, 1316 – 1334. 3) P. Klahn, M. Brönstrup, *Nat. Prod. Rep*., **2017**, *34*, 832 – 885. 4) K. Ferreira et al., *Angew. Chem. Int. Ed.* **2017**, *56*, 8272-8276. 5) L. Pinkert, et al. *J. Med Chem.* **2021**, *18*, in press. 6) W. Tegge et al., *Angew. Chem. Int. Ed.* **2021**, *60,* 17989-17997.

PL-5

Illuminating New Pathways in Biology and Anti-Bacterial Drug Development Using Small Molecules

Prof. Jason K. Sello

Department of Pharmaceutical Chemistry
University of California, San Francisco

Much high-impact research in the chemical and biological sciences, particularly that which underlies innovations in medicine, began with curiosity about the structures and mechanisms of bioactive small molecules. In search of potentially transformative discoveries, my research group is focused on molecules that are anomalous by virtue of their structures and the mechanisms by which they perturb biological systems. The seminar will describe how our recent studies of such molecules have yielded new insights into the structures and functions of chaperone-dependent proteases that enable protein homoeostasis in bacteria. It will also highlight how these studies are the bases of compelling leads for first-in-class anti-bacterial drugs.

PL-6

Diversity to Discovery - A Senrendipitous 'Golden' Entry into Glycochemistry

Prof. Srinivas Hotha

Department of Chemistry, Indian Institute of Science Education and Research, Pune – 411008, MH

Gold and sugar allured Mankind for many centuries and continue to impact economics even now. A series of serendipitous observations during 2005-06 in the group culminated into the discovery of a novel glycosylation protocol by amalgamating the elegance from the chemistry of gold with that of saccharides.[1] Thus identified procedure has undergone several iterative modifications over the last decade to make it versatile.[2] The latest protocol of alkynyl carbonate donors from the group has opened a new vista of opportunities for the syntheses of giant oligosaccharides which are otherwise quite challenging to accomplish.[3]

To exemplify, the glycocalyx of *Mycobacterium tuberculosis* comprising xenobiotic arabinofuranose and galactofuranose was targeted. Combining the bioinspired stereoselective synthesis of 1,2-*cis* and *trans* furanosides and the new glycosidation method, the synthesis of a heneicosasaccharide containing 19 Ara*f* residues and 2 Gal*f* residues,[4] and a pentacosasaccharide[5] containing 23 Ara*f* residues and 2 Gal*f* residues was accomplished. In addition, a patent non-infringing complex glycosaminoglycan drug Arixtra® was also demonstrated by our methods.[6] The synthesis of highly branched, complex and challenging Hentriacontahectanosyl Arabinongalactan and Lipoarabinomannan is currently underway in the group. The path to the discovery, development of the protocol for glycosidation and how they impact the work of medicinal chemistry directly as well as infectious diseases in an indirect manner will be discussed during the seminar.

1. Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620-9621.
2. Kayastha, A. K.; Hotha, S. *Chem. Commun.* **2012**, *48*, 7161-7163.
3. Mishra, B.; Neralkar, M.; Hotha, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 7786-7791.
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   Walke, G.; Kasdekar, N.; Sutar, Y.; Hotha, S. *Communications Chem.* **2021**, *4*, 15 (*https://doi.org/10.1038/s42004-021-00452-y | www.nature.com/commschem)*

Invited Lectures (IL)

IL-1

Drugs for bad bugs: Progress amongst challenges

Dr. Siddharth Chopra

CDRI, Lucknow

Antimicrobial resistance has been internationally recognized as a significant threat to healthcare systems worldwide. Due to multiple reasons including unfavorable economics, increasing emergence of drug-resistant bacteria and expensive and lengthy clinical trials, most of the big pharma has exited the discovery and development of new anti-infectives. In order to augment the non-existent to depleted drug-discovery pipeline targeting drug-resistant bacteria, our lab follows 2 complimentary approaches: conventional phenotypic whole cell screening of diverse chemical scaffold libraries as well as natural products and drug-repurposing of FDA approved drugs for new clinical uses. In my talk, I will discuss and highlight the challenges which we face along with some success stories which have come out of my lab. The talk will highlight the core issue: Drug discovery against drug-resistant microbes is an extremely interdependent, interconnected battle involving multiple expertise's against a very intelligent, ruthless and adaptable adversary.

IL-2

A Chemical Approach for the Development of Novel Antibacterial Agents

Ishu Saraogi, Ph.D.

Department of Chemistry & Department of Biological Sciences, IISER Bhopal, Bhopal, 462066, India

Our research at the interface of chemistry and biology, focuses on the use of chemical approaches for the development of novel antibacterial agents. In my talk, I will summarize our work in this area using two examples.

Bacterial resistance to antibiotics poses an unprecedented challenge to global health. In search of novel antibacterial strategies capable of evading existing resistance mechanisms, we identified the bacterial signal recognition particle (SRP), an essential protein transport machinery, as a potential target. Functional SRP is composed of a protein (Ffh) and a 4.5S RNA component, so we envisioned that antisense peptide nucleic acid (PNA) molecules targeting 4.5S RNA might inhibit the RNA-Ffh interaction, thus compromising bacterial viability. Designed PNA molecules indeed bound specifically to 4.5S RNA, and inhibited the 4.5S RNA-Ffh interaction in a dose dependent manner, leading to inhibition of SRP mediated GTP hydrolysis. The most potent PNA molecule, when tagged with a cell penetrating peptide, was able to effectively inhibit *E. coli* cell growth. The PNA-mediated inhibition was relieved by overexpression of 4.5S RNA, suggesting that the PNA specifically blocks 4.5S RNA function. Our work validates SRP as an antibacterial target for the first time, and invites research into small molecule inhibitors of bacterial SRP as potential antibacterial agents.

Molecular chaperones play an essential role in maintaining proteostasis in the cell. The bacterial chaperone DnaK, a homologue of heat shock protein (Hsp70), actively holds or unfolds thermosensitive proteins and prevents their misfolding and aggregation. DnaK is essential under stress, and is thus an attractive antibacterial target. Using an in-house small molecule library screening approach, we identified a synthetic molecule M7 as a potential inhibitor of DnaK. Competitive binding studies with a substrate peptide suggest that M7 likely binds at the DnaK substrate-binding domain, and inhibits ATPase and luciferase refolding activity of DnaK. Using bacterial growth assay and biofilm assay, we show that M7 inhibits the *P. aeruginosa* growth and biofilm formation. SEM and confocal imaging suggest that M7 could permeate bacterial cells and inhibit growth, while itself being non-toxic to HEK cells. Thus, M7 is a very promising lead molecule for DnaK inhibition.

IL-3

Glycosylphosphatidylinositol-linked aspartyl proteases: Multifunctional enzymes and key mediators of *Candida glabrata*-host interaction

Dr. Rupinder Kaur

Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad

The human opportunistic fungal pathogen *Candida glabrata* possesses a family of eleven putative glycosylphosphatidylinositol (GPI)-linked, cell surface-associated aspartyl proteases that are essential for its virulence. These proteases are commonly referred as yapsins, and assumed to contain two aspartic acid residues in their catalytic site. *C. glabrata* yapsins are encoded by *CgYPS1-11* genes that reside on three different chromosomes, Chromosome A, E and M. We are interested in elucidating the molecular basis underlying multiple roles that Cgyapsins perform in physiology and pathogenesis of *C. glabrata*. Towards this end, we have uncovered some expected and some unanticipated functions of CgYapsins, which range from regulation of cell wall organization and survival of diverse stresses to maintenance of pH and vacuole homeostasis. Additionally, we have shown that CgYapsins are required for suppression of the pro-inflammatory immune response in host macrophages, and modulation of the *C. glabrata* secretome. These findings along with the identified substrates of GPI-anchored aspartyl proteases in *C. glabrata* will be presented.

IL-4

Use of indomethacin in Covid 19 patients

Dr. Ravichandran Rajan

MIOT International, Chennai.

Indomethacin is a time honored anti inflammatory drug used in rheumatoid arthritis. It is a prostaglandinE synthase inhibitor and Cathepsin L inhibitor. Interestingly this has a powerful antiviral action against cytomegalovirus vesicular herpes virus and corona virus. It is the only drug which has a combination of anti inflammatory, anti viral and anti platelet action. The presentation involves our experience of indomethacin in 4 studies. Two of them refer to our experience of treating a small number of covid -19 patients in high risk situation like chronic kidney disease, kidney transplantation, diabetes, obesity etc. The third one is a registerd clinical trial done in august 2020 - use of indomethacin in mild and moderate covid patients with a propensity score matching using paracetamol in the other arm.

All the patients in the indomethacin group recovered by day 4 with only one patient requiring oxygen for 2 days. This was grossly different from the paracetamol group where symptoms took longer to resolve and 34% developed hypoxia requiring oxygen. In the same study 22 patients with severe covid were treatedt with remdesivir and indomethacin, All showed a full recovery by 14 days without mortality or ventilator support. The fourth study is the most important one done in may 2021 when already the mutant strain was present - A Randomised control study involving 100 patients in each arm. Once again the difference from the paracetamol arm was grossly significant in terms of recovery of symptoms or development of hypoxia. The drug was found safe in all four studies without deterioration of kidney or liver functions.

In conclusion indomethacin needs to be used as the first line of treatment in covid-19 patients with very few contraindications

This would be a cheap and effective way of avoiding hospitalization, and reducing the spread since cough is well controlled Considering the scientific basis and the clinical experience it would be effective in treating mutant strains also.

IL-5

Dr. Anoop Kumar,
BM Hospitals, Kozhikode

To be Announced

IL-6

The role of viral membrane proteins in enveloped virus budding and development of antivirals

Debajit Dey, Subhomoi Borkotoky, Ramesh Kumar, **Manidipa Banerjee**

Kusuma School of Biological Sciences, Indian Institute of Technology Delhi, Hauz Khas, New Delhi – 110016, India

Although different virus families have distinct mechanisms for host interaction, there exists striking similarities in these processes which can be exploited for repurposing or development of broad range antivirals. One example is viroporin mediated membrane alteration/remodelling for facilitating replication and egress of enveloped viruses from infected cells. We are characterizing two viroporins (viral membrane proteins) from Chikungunya Virus and SARS-CoV-2, which are essential for virus budding. The 6K protein of Chikungynya Virus forms ion channels in membranes that can be blocked by amantadine, a generic inhibitor of other virally encoded, channel forming proteins. Although 6K has the propensity to localize in ER membranes, it appears to relocate to the plasma membrane in presence of the viral glycoprotein E2. The translation of 6K from CHIKV genome is accompanied by ribosomal slippage leading to production of a transframe variant (TF), whose role in CHIKV biology is under investigation. Our data indicates that TF interacts with the tight junction protein Scribble through a PDZ domain binding motif at its C-terminus. We propose that the disruption of cellular tight junctions by the interaction of CHIKV TF with Scribble facilitates virus spread. The Envelope protein (E) of SARS-CoV-2 is a functional analogue of CHIKV 6K and is also required for virus budding and pathophysiology. The essential roles of 6K/TF and E in budding and egress of progeny viruses indicate that they may be excellent targets for development of broad-spectrum antivirals.

IL-7

Outwitting antibiotic resistance: A perpetual battle

Dr. Jayanta Haldar

Professor, Antimicrobial Research Laboratory, New Chemistry Unit and School of Advanced Materials**,** Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR)**,** Jakkur, Bangalore 560064, India.

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Antimicrobial resistance (AMR) currently claims around seven hundred thousand lives annually and this is expected to rise to ten million by 2050 if not tackled immediately. India is the highest contributor to this staggering statistic. The increasing emergence of resistance towards antibiotics, and the complications in infection prevention and cure which arise thereof, call for thorough scientific investigations. As arsenal of effective antibiotics dwindle, more and more effort is being focussed on the development of novel strategies to tackle drug resistant bacteria. This talk involves our efforts towards mitigation of problems created due to antimicrobial resistance and complex infections. The development of synthetic small moelcular and macromolecular mimics of antimicrobial peptides with different mechanism action compared to most of the conventional antibiotics as an alternative class of antibacterial agents will be discussed.[1,2] Our group has immensely contributed to developing various vancomycin analogues, which display highly enhanced activity against vancomycin-resistant *S. aureus*, vancomycin-resistant *E. faecium*, as well as other Gram-positive and Gram-negative pathogens. The novel approaches to overcome bacterial resistance towards glycopeptides, via semisynthetic modifications will also be discussed.[3-5] With the view of rehabilitation of the shelved out, inactive antibiotics, our lab is working on developing antibiotic adjuvants, i.e. agents which, when used in combination with the obsolete or ineffective antibiotic, will repurpose or reactivate the antibiotic against clinically relevant superbugs.[6]

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IL-8

Opening up anti-malarial Drug Discovery

Dr. Kirandeep Samby Kaur

Medicines for Malaria Venture

Malaria elimination has been reinstated as a global health priority and at MMV we are working to Discover, develop and deliver safe, effective and affordable antimalarial medicines to the most vulnerable populations. Drug discovery is a long and challenging process and new ways of working together and catalyse ideas must be identified. In the talk, case studies showcasing these models will be discussed

IL-9

Mycobacteria's smart arsenals: Role of Small Intermediary metabolites (SIMs)

Dr. Vani Janikiraman

Department of Biotechnology, *IIT, Madras.*

The two important aspects of an infection include the incoming pathogen and the defending host immune system. *Mycobacterium tuberculosis* (Mtb) is an intra-cellular pathogen that has developed specific mechanisms to invade and survive within its host cells. Immunomodulation in tuberculosis by Mtb has been discussed only as a virtue of the pathogen; however, the mechanistic intricacies of the pathogen mediators of immune response alterations have received less attention. Several bacterial proteins have been scrutinized for their immunogenicity since proteins are known to be antigenic in comparison to other macromolecules. However, virulence of Mtb has also been ascribed to a plethora of cell surface lipid moieties for their abundance in the Mtb cell wall. Whilst such large macromolecules and surface associated signatures have often received the deserving attention, the role of small secondary metabolites (SIMs) synthesized by the pathogen and their consequence on the host-mycobacteria balance has remained elusive. This talk will discuss preliminary results towards identification of such alternative bacterial mechanisms that may contribute to subversion of host responses allowing better survival with least fitness cost to the host.

IL-10

Probing into genome and proteome maintenance pathways in the human malaria parasite for design of alternative intervention strategies.

Dr. Niti Kumar
CSIR-Central Drug Research Institute Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, Uttar Pradesh, India

Human malaria parasite, *P. falciparum* harbors an AT-rich (>80%) genome which codes for a metastable and aggregation-prone proteome. Despite the vulnerability to genotoxic and proteotoxic stress, the parasite is able to maintain cellular homeostasis during hostile conditions and withstand immune threats mounted by mosquito vector and human host. We are trying to understand distinct genome (telomere homeostasis) and proteome (proteostasis) maintenance pathways which gives a competitive-edge to the malaria parasite.

The premise of the talk includes

(a) Understanding non-canonical nucleic acids structures and telomere homeostasis. Can small-molecule based targeting of non-canonical nucleic acid structures in telomeric ends be an alternative intervention strategy?

(b) Probing structural and functional diversity of protein folding and degradation machinery in malaria parasite. Has the parasite evolved diverged protein quality control machinery which minimizes protein misfolding and efficiently remove aggregates?

IL-11

Identifying crucial E-protein residues responsible for unusual stability of Zika virus envelope

Prof. Sanjib Senapati

Department of Biotechnology, IIT Madras.

Outbreak of zika virus (ZIKV) infections in 2015-16 that caused microcephaly and other congenital abnormalities in newborns prompted intense research across the globe. These studies have suggested that ZIKV can sustain high temperatures and harsh physiological conditions, unlike the other flaviviruses such as dengue virus (DENV). In contrast, recent cryo-EM studies have shown very similar architecture of the ZIKV and DENV envelopes that constitute the primary level of viral protection. Encouraged by these findings, we attempted to identify the crucial protein residues that make the ZIKV envelope so robust by employing coarse-grained and all-atomic molecular dynamics simulations, and computational mutagenesis studies. In accordance with more recent cryo-EM findings, our simulation results exhibited stable ZIKV envelope protein shell both at 29^{o} and 40^{o}C, while the DENV2 shell loosened up significantly at 40°C. Subsequently, we simulated a series of ZIKV variants to identify the specific domain and residues involved in maintaining the structural integrity of the viral protein shell at high temperatures. Our results suggest that the DIII domain, more specifically, the CD- and FG-loop residues of the ZIKV protein shell play a crucial role in making the virus envelope thermostable by inducing strong raft-raft interactions. These findings can accelerate the rational design of ZIKV therapeutics.

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IL-12

Target Repurposing for A New Virus: Tinkering Endosomal Toll-Like Receptors

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The pathogenesis of SARS-CoV-2 and the role of adaptive and innate immune system are still under investigation. Evolutionary conserved toll-like receptors (TLRs) play a major role in the initiation of innate immune responses, inducing antiviral response by triggering the production of inflammatory cytokines, type I IFN and other mediators. Upon activation, TLR7 and TLR9 present in endosomal compartment releases IFN-α and other proinflammatory cytokines, which exercises multiple immune modulatory and antiviral activities. In particular, TLR7, TLR8 and TLR9 can recognize viral ssRNA and CpG DNA. Recently, IFN-α level has been shown to play a critical role in the pathogenesis of patients progressing to severe COVID-19 conditions. In view of that, TLR7 and TLR9 could be potential targets in controlling the COVId-19 as well as production of vaccine against SARS-CoV-2. Agonists of these TLRs are in clinical development for their ability to augment the immune response and play a critical role in treatment of different types of cancer and virus mediated infectious diseases. Whereas, antagonists are implicated during aberrant activation of immune system is implicated in various autoimmune diseases such as systemic lupus erythematosus, psoriasis, Sjogren's syndrome etc. Thus, both receptor agonists and antagonists are double edge sword useful in different clinical contexts is being sought for globally.

Our lab has been long involved in the development of TLR7 and TLR9 modulators. Through various drug-discovery strategies, our lab has discovered and developed different scaffolds with TLR9/7 antagonism, first-of-its-kind to our knowledge. We ended up developing clinically relevant TLR9/7 antagonist with favourable pharmacokinetics and oral bioavailability in mice. To further validate the in vivo applicability of this novel TLR9/7 antagonist, we demonstrated its excellent efficacy in a preclinical disease model. The talk will be divided into two parts. The first part includes, repurposing of 'TLRs as target' in COVID-19. The second part will cover various strategic medicinal chemistry approaches for discovery and development of TLR7 and TLR9 modulators of clinical significance.

Mini Oral Presentations

Abstracts

P-1

Synthesis, characterization and theoretical studies on Pd(II) thiocarbohydrazone complexes and their biological implications using *in silico* molecular docking

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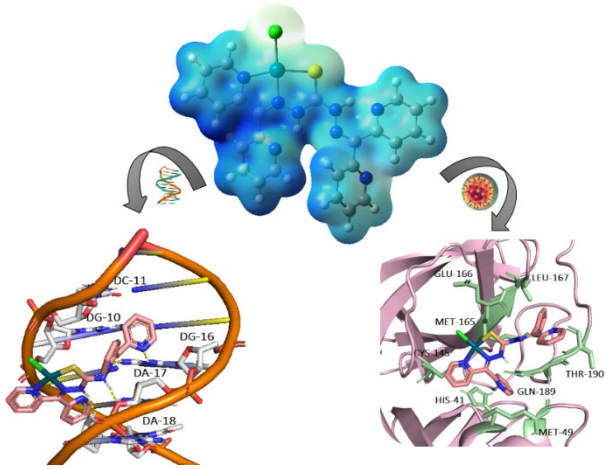
Palladium(II) complexes are potential biological candidates owing to their structural and thermodynamic similarities to Pt(II) anticancer complexes. We have recently reported the binding efficiencies of a thiocarbohydrazone and its Mn(II) complex against SARS-CoV-2 main protease[1]. Here we report the synthesis and physico-chemical characterization of two novel Pd(II) complexes derived from 1,5-bis(2-benzoylpyridine)thiocarbohydrazone and 1,5-bis(di(2-pyridyl)ketone)thiocarbohydrazone. The band gap (E_g) of the complexes were determined experimentally using Kubelka-munk model and theoretically by DFT quantum chemical calculations. The DFT studies of the complexes were carried out using B3LYP/6-311G (d,p) and LanL2DZ basis sets. *In silico* molecular docking studies of the complexes were performed with B-DNA dodecamer (1BNA), which confirm their efficacy as a potential DNA binder. Nevertheless, the docking studies with active sites of the SARS-CoV-2 viral protease reveal their propensity towards the latter also. The docking scores of the Pd(II) complexes were found better than that of some of the repurposed drugs such as chloroquine, hydroxychloroquine, remdesivir and favipiravir.



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P-2

Immunopharmacological evaluation of Th1 adjuvants with MF59 against SARS-COV-2 Spike S1 antigen.

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Corona virus disease 2019 (COVID 19) is a rising infectious disease belonging to *Coronaviridae* family [1]. Severe acute respiratory syndrome Corona virus 2 (SARS-COV-2) emerged in December 2019 in the city of Wuhan, Hubei province of China [2]. World Health Organization's declared Corona virus disease 2019 (COVID-19) pandemic [3]. Around 19-21 vaccines are currently in clinical use among which 10-12 are adjuvanted vaccines. The major objective behind our study was to evaluate the efficiency of various PRRs and TCR ligand-based adjuvants along with MF59 against SARS COV-2 antigen. From the data obtained we can conclude that all these adjuvants at various concentrations of 10, 20 and 30µg have elicited a potent antibody (10-15 folds) and cellular response against SARS-COV-2 antigen. All the Th1 effectors at different concentration had a varying degrees adjuvanticity against specific antigens, thus, the data obtained gives clues of the gross response of these adjuvants but a more in-depth study of these systems is very essential for developing a successful vaccine candidate against SARS-COV-2.

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P-3

An Approach for the Generation of γ-Propenylidene-γ-butenolides and Application to the Total Synthesis of Rubrolides

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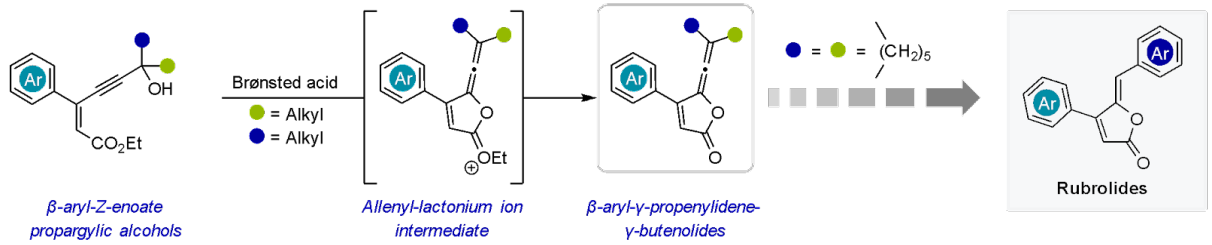
Allenes are ubiquitously encountered in many bioactive natural products[1] and have served as important functional group for the development of many novel synthetic methodologies.[2] Due to this wide applicability ample synthetic strategies have been devised for the efficient synthesis of structurally diverse allenes.[3] The present poster will delineate a strategic approach towards a new class of γ-butenolides, *viz.* β-aryl-γ-propenylidene-γ-butenolides and their subsequent synthesis from β-aryl-Z-enoate propargylic alcohols in presence of Brønsted acid. Isolation of β-aryl-γ-propenylidene-γ-butenolides and their ^{18}O-isomer confirmed the intermediacy of the allenyl-lactonium ion as well as the cyclic-hemiacetal during the proposed mechanism. Utilization of the β-aryl-γ-methylenecyclohexenylidene-γ-butenolides as starting materials offered a highly stereoselective and efficient access towards the frameworks of rubrolide natural products. The practical application of this novel strategy has been showcased by achieving the total synthesis of rubrolideE.[4]



Scheme 1. Acid promoted access to structurally unique γ-propenylidene-γ-butenolides

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P-4

Molecular Docking Studies of Some Naturally Occurring Flavonoids Against SARS CoV-2 Receptors

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Flavonoids are an important kind of natural product. Flavonoids are a diverse group of phytonutrients (plant chemicals) found in almost all fruits and vegetables. Along with carotenoids, they are responsible for the vivid colors in fruits and vegetables. They have miscellaneous reciprocal biochemical and antioxidant effects associated with various diseases such as cancer, Alzheimer's disease and atherosclerosis. It is due to antioxidants, anti-inflammatory, antimutagens and anti-cancer-causing properties combined with the ability to control major cell enzyme functions. Intriguingly, some flavonoids also have antiviral activity. Currently, there is no appropriate treatment for SARS-CoV-2 or vaccine alive to care for humans from such infections. It is extremely urgent to build up numerous therapeutic agents for SARS-CoV-2 virus because of its high infection, morbidity and its ability to cause epidemics universally. In addition, the primary drug discovery pipeline we introduced to the molecular docking studies against important target proteins like a spike, SARS Cov-2-M^{pro}, SARS CoV $3CL^{pro}$ and ACE-2 protein, can be potential druggable targets. From the literature studies it is clear that flavonoids having antiviral activity, in the present study we have selected three naturally occurring flavonoids such as: Quercetin(7A), Fisetin(7B) and Rutin(7C) for docking studies. The docking study compared with currently used human trial drugs such as Hydroxychloroquine, Favipiravi and Lopinavir/ritonavir

METHODOLOGY: The docking procedure was established to study the binding affinity of some flavonoids with major proteins found in SARS-CoV 2 virus. The chemical structures of different flavonoids were obtained from the PubChem database. The crystallographic structures of SARS-CoV-2 Mpro (6LU7), SARS-CoV 3CLpro(1UK4), ACE2 receptor(6MOJ) and NSP 12 RNA Polymerase(6NUR) are obtained from RCSB.PDB database. Then we studied the protein-ligand interactions using the docking procedure (Chimera and Autodock vina). Considering the medicinal importance of the flavonoids derivatives, additional drug likeness properties are calculated from the SwissADME. SwissADME calculation indicated that all have good hydrogen bonds donor or acceptor. Among the sequence of compounds, 7A ligand showing binding energy against four [6LU7, 1UK4, 6MOJ and 6NUR] proteins with binding energies -7.2kcal/mol, -8.9kcal/mol, -8.4kcal/mol and -8.6kcal/mol respectively. 7Bligandshowing binding energy against four [6LU7, 1UK4, 6MOJ and 6NUR] proteins with binding energies -7.4 kcal/mol, -8.9 kcal/mol, -8.5 kcal/mol and -8.2 kcal/mol respectively. 7C ligand showing binding energy against four [6LU7, 1UK4, 6MOJ and 6NUR] proteins with binding energies -7.7kcal/mol, -8.5kcal/mol, -7.9kcal/mol and -8.3 kcal/mol respectively. The docking results were compared with human trial drugs such as hydroxychloroquine (HQC), favipiravir and lopinavir. The outcome gives information to show an excellent result on COVID-19 proteins.

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P-5

Synthesis and cytotoxicity evaluation of a 'V-shaped' fluorescent 4-Amino-1,8-naphthalimide Tröger's base derived Ru(II)-curcumin organometallic conjugate

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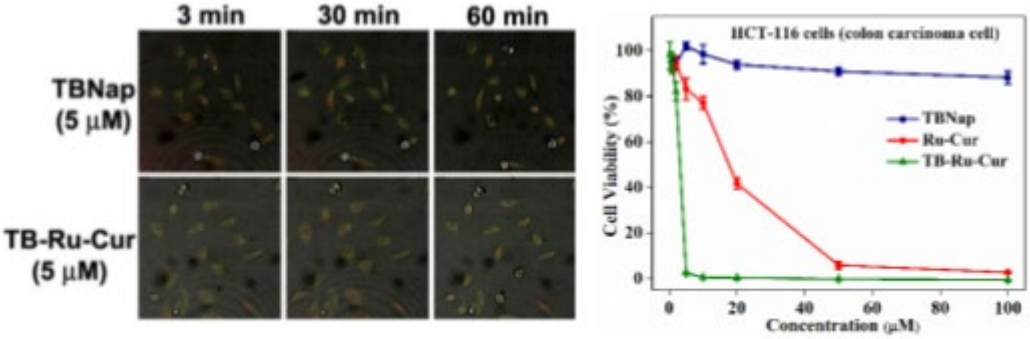
The design, synthesis and application of luminescent metal complexes as efficient theragnostic agents have great significance in the field of medicinal chemistry [1]. Luminescent *d*-metal ion complexes are well-known for their therapeutic activities because of their unique photochemical and photophysical characteristics [2]. 4-amino-1,8-naphthalimide derived Tröger's base (**TBNap)** derivatives are novel organic scaffolds that are famous for their robust DNA binding affinity, quick cellular uptake, and can also act as apoptosis inducers in cancer cells [3-5]. We have developed a novel luminescent *N*-4-pyridyl-4-amino-1,8-naphthalimide Tröger's base (**TB Nap**) with unique chiral cleft shape geometry using N-4-pyridyl-4-amino-1,8-naphthalimide as the precursor through facile synthetic strategy. Knowing the significance of ruthenium metal complexes and the naturally available therapeutic agent "curcumin" and **TBNap** in the field of cancer therapy, we designed a novel **TBNap**-containing Ru(II) curcumin organometallic conjugate **(TB-Ru-Cur)** by the self-assembly of **TBNap** with previously reported arene-Ru(II)-curcuminato complex, **Ru-Cur**. **TB-Ru-Cur** displayed a fast cellular uptake, highly luminescent characteristics, and cytotoxicity against various cancer cell lines such as HeLa cells, HCT-116, and HepG2 cancer cells with an efficiency much higher than clinically used cisplatin. In summary, the work herein demonstrates that the **TB-Ru-Cur** can act as a potent anticancer theragnostic agent thereby bridging the gap between therapeutic and diagnosis properties.



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P-6

Optimal Balance of Hydrophobic Content and Degree of Polymerization Results in a Potent Membrane Targeting Antibacterial Polymer

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Globally, excessive use of antibiotics has drastically raised the resistance frequency of disease-causing microorganisms among humans, leading to a scarcity of efficient and biocompatible drugs[1]. Antimicrobial polymers have emerged as a promising candidate to combat drug-resistance pathogens[2]. Along with the amphiphilic balance, structural conformation and molecular weight (Mn) play an indispensable role in the antimicrobial potency and cytotoxic activity of polymers. Here, we synthesize cationic and amphiphilic methacrylamide random copolymers using free-radical copolymerization. The mole fraction of the hydrophobic groups is kept constant at approximately 20% while the molecular weight (average number of linked polymeric units) is varied and the antibacterial and cytotoxic activities are studied. The chemical composition of copolymers is characterized by ^{1}H NMR spectroscopy. We observe that the average number of linked units in a polymer chain (i.e., molecular weight) significantly affects polymers activity and selectivity. The antibacterial efficacy increases with increasing molecular weight against both the examined bacteria *E. coli* and *S. aureus*. Bactericidal activity of polymers is confirmed by live/dead cell viability assay. Polymers with high molecular weight display high antibacterial activity yet are highly cytotoxic even at 1× MIC. However, low molecular weight polymers are biocompatible while retaining antibacterial potency. Furthermore, no resistance acquisition is observed against the polymers in *E. coli* and *S. aureus.* A comprehensive analysis using confocal and SEM techniques shows that the polymers target bacterial membranes, resulting in membrane permeabilization that leads to cell death.

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P-7

Arsenic Toxicity: Carbonate's Counteraction Revealed

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Well-known purification technologies built for arsenic (As) removal from drinking water are not sustainable, either being unaffordable or inefficient in the elimination of traces of As. In our experiments, we observed that carbonate ion can counteract the effects of As exposure as it efficiently prevented As-induced cytotoxicity on epithelial cell lines of the small intestine (IEC-6). The cotreatment of IEC-6 cells with 40 ppm of carbonates and As (≥3 ppm) showed substantial remissions in the As-induced cytotoxicity and increased the viability from 50% to 75%. The production of intracellular reactive oxygen species (ROS) and cellular acidification were also reduced in this process (pH increase from 5 to 6.5). Thus, the present study suggests that the cytoprotective effect of carbonate can involve multiple pathways, such as reduction of extracellular/intracellular acidosis, H_2O_2 decomposition, balancing mitochondrial potential, and immobilization of As. We show that As-contaminated drinking water enriched with carbonates up to 40 ppm has a reduced toxic effect on cells in comparison to that of an As-alone sample. Therefore, carbonates can act as an adjunct in addition to the prevailing approaches to tackle mass poisoning by As. We believe that this study is initial evidence for developing an alternative method to tackle the prevailing mass environmental poisoning by As, using locally available, affordable, safe, and sustainable solutions.

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P-8

Ambient mass spectrometry using electrospun nanofibers to collect molecular information from plants and visualisation of infectional contamination growings on fruits

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Keywords: *Electrospinning, Nanofibers, DESI-MS, Smart Surfaces, and Imprint Imaging.*

In this work, an ambient ionisation mass spectrometry, DESI MS-based molecular analysis and imprint imaging using electrospun nylon-6 nanofiber mats are demonstrated for various analytical contexts. Uniform mats of varying thicknesses composed of ~200 nm diameter fibers were prepared using needleless electrospinning. Analytical applications requiring rapid understanding of the analytes in single drops, dyes, inks, and/or plant extracts incorporated directly into the nanofibers are discussed with illustrations. The possibility to imprint patterns made of printing inks, plant parts (such as petals, leaves, and slices of rhizomes), and fungal growth on fruits with their faithful reproductions on the nanofiber mats is illustrated with suitable examples. Metabolites were identified by tandem mass spectrometry data available in the literature and in databases. The results highlight the significance of electrospun nanofiber mats as smart surfaces to capture diverse classes of compounds for rapid detection or to imprint imaging under ambient conditions. Large surface area, appropriate chemical functionalities exposed, and easiness of desorption due to weaker interactions of the analyte species are the specific advantages of nanofibers for this application.

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P-9

Lysine acetylation in Hsp16.3: Effect on its structure, chaperone function and growth of *Mycobacterium tuberculosis*

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Tuberculosis is considered as one of the major global human affliction over the past decades with increasing human morbidity and mortality. *Mycobacterium tuberculosis* is the etiological agent of this disease, which secretes a major immunodominant antigen namely Hsp16.3, throughout the course of infection. This protein belongs to the member of small heat shock protein (sHsp) family. Its molecular chaperone function plays a pivotal role in the growth and survival of *Mycobacterium tuberculosis* pathogen during the latency of infection. Inside this pathogen, Hsp16.3 encounters various post-translational modifications. Among these post-translational modifications, lysine acetylation is a vital one, and various lysine (K) residues (K64, K78, K85, K114, K119, K132 and K136) in *Mycobacterium tuberculosis* Hsp16.3 have been found to be acetylated *in vivo*. But, the impact of lysine acetylation on the structure and function of Hsp16.3 as well as on the growth of *M. tuberculosis* is far from clear. We employed site directed mutagenesis approach so as to understand the effect of lysine acetylation of Hsp16.3 on its structure and chaperone function. Beside this, the effect of lysine acetylation in Hsp16.3 on growth of *M. tuberculosis* H37Ra strain was also examined. First, we over-expressed and purified the wild-type Hsp16.3 and eight “lysine acetylated” mimic mutant proteins of Hsp16.3 [Hsp16.3-K64Q, Hsp16.3-K78Q, Hsp16.3-K85Q, Hsp16.3-K114Q, Hsp16.3-K119Q, Hsp16.3-K132Q, Hsp16.3-K136Q (all of them resemble acetylation of individual lysine residue) and Hsp16.3-K64Q/K78Q/K85Q/K114Q/K119Q/K132Q/K136Q (resembles the acetylation of all these seven lysine residues together)]. All these "lysine acetylated" mimic mutants possess different secondary and tertiary conformation than the wild type protein. Mutation of individual lysine residues to glutamine (K64Q, K78Q, K85Q, K132Q, and K136Q) and all the seven lysine residues together to glutamine at a time (K64Q/K78Q/K85Q/K114Q/K119Q/K132Q/K136Q) led to the dissociation of oligomeric assembly of Hsp16.3. Five acetylation mimic mutants (Hsp16.3-K64Q, Hsp16.3-K78Q, Hsp16.3-K85Q, Hsp16.3-K132Q, and Hsp16.3-K136Q) have higher surface hydrophobicity, whereas other three mutants (Hsp16.3-K114Q, Hsp16.3-K119Q and Hsp16.3-K64Q/K78Q/K85Q/K114Q/K119Q/K132Q/K136Q) have lower surface hydrophobicity as compared to the wild type Hsp16.3. Some of these "lysine acetylated" mimic mutants (K64Q, K78Q, K85Q, K132Q, K136Q and K64Q/K78Q/K85Q/K114Q/K119Q/K132Q/K136Q) enhances the chaperone function of Hsp16.3 as well as retard the growth of *M. tuberculosis* H37Ra strain, indicating that *in vivo* acetylation may possibly improve the chaperone function of Hsp16.3 as well as may help the pathogen to grow slowly in latent phase of tuberculosis. This particular study shows the possible

physiological roles of lysine acetylation in *M. tuberculosis*. As the chaperoning ability of mycobacterial antigenic proteins are directly correlated with their efficacy in boosting BCG vaccines, those Hsp16.3 mutant variants having better chaperone function could possibly be utilized for effective boosting of BCG vaccines.

P-10

Naturally Occurring Chiral 2-Hydroxycitric Acids in the Construction of Molecules of Drug-likeness

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Chiral molecules, either obtained directly from nature or through chemical modification of the naturally occurring molecules, play a vital role in the pursuit of pharmaceutical and synthetic organic chemistry. Those molecules isolated from various sources often exhibit diverse biological activities, and exemplified by their pivotal role in the scope of chemical biology, drug discovery, and drug development. Among various strategies toward the synthesis of enantiopure compounds, the chiral pool approach is extremely attractive due to assured optical purity of the target molecule, and economic viability. Several tropical plants are rich sources of structurally simple chiral 2-hydroxycitric acids. Out of the four possible optical isomers, the (2*S*,3*S*)-diastereomer garcinia acid and the (2*S*,3*R*)-diastereomer hibiscus acid have been isolated as their *γ*-butyrolactones in optically pure form in kilogram quantities. The two stereogenic centers in these *γ*-butyrolactones have structural and stereochemical features that relate to several small bioactive molecules of synthetic or natural origin. However, using the molecules having a three- or four-carbon framework, synthesis of target molecules with a basic skeleton having more than four carbons inevitably involves lengthy synthetic sequences. Therefore, the chiral lactones of garcinia and hibiscus acids bearing chemically amenable functional groups, could be an ideal choice for the diversity-oriented construction of several bioactive compounds such as (-)- and (+)-crispine A,[1] (+)- and (−)-harmicine, bicyclic furo[2,3-*b*]pyrrolo skeleton, pyrrolidine-2,5-diones.[2] A novel strategy have been developed for the synthesis of fused bis-THF moiety of anti-HIV drug Darunavir employing garcinia acid. This method is operationally simple, economically viable and superior to some of the existing methods.[3] Using this new chiral hexahydrofuro[2,3-*b*]furan-3-ol, attempts were made towards the total synthesis of an analog of Darunavir. Accordingly, the uniqueness of relatively cheap, naturally occurring chiral 2-hydroxycitric acid lactones as Chiron has been demonstrated by the construction of some important organic small-molecules of drug-likeness, which are otherwise difficult to synthesize.

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P-11

Structural dynamics of ATP and inhibitor bound receptor tyrosine kinase to explore open and closed states

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Receptor Tyrosine Kinases (RTKs) are ubiquitous trans-membrane components of cellular signalling transduction pathways. A precise ligand recognition of the extracellular region leads to receptor dimerization and downstream signalling events that communicate a cascade of cellular communication pathways. The RTK activation leads to control of protein expression, regulate the normal physiological events in cell survival, proliferation, growth and death. Overexpression of these RTKs could lead to activation of abnormal cascade of signalling pathways which cause numerous effects on cellular role of proteins and their activity. It is interesting to study RTKs that are responsible for several cancer forms and therefore to design their inhibitors. We have studied the Tyro3, Axl and Mer (TAM) kinases by homology structure modelling and docking of reported inhibitors and ATP co-factor. All atomic molecular dynamics (MD) simulations of microsecond timescale and longer provide robust insights into the structural details of conformational alterations of proteins due to their role in cellular metabolic activities and signaling pathways. The analyses of these post MD simulation trajectories of protein dynamic conformational changes revealed the kinase allosteric activity during inhibitor and ATP binding mode at kinase active site. Cabozantinib, a small molecule inhibitor constrains the activity of TAM kinases at nanomolar concentrations. For consensus, the 1µs atomistic simulations with enhanced computational algorithms to generate the dynamic active and inactive conformations of kinases are play a crucial role in inhibitor binding and the activation of intracellular downstream signaling pathways.. In this current study we report microsecond molecular dynamics (MD) simulations of apo, ATP and cabozantinib bound active and inactives states of TAM RTKs and analysed theses post-MD trajectories using the principal component analysis (PCA). Markov State Models (MSM) and transition pathway models from Perron-cluster cluster analysis.

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P-12

Cascade C-N Cross-Coupling under solvent-free conditions

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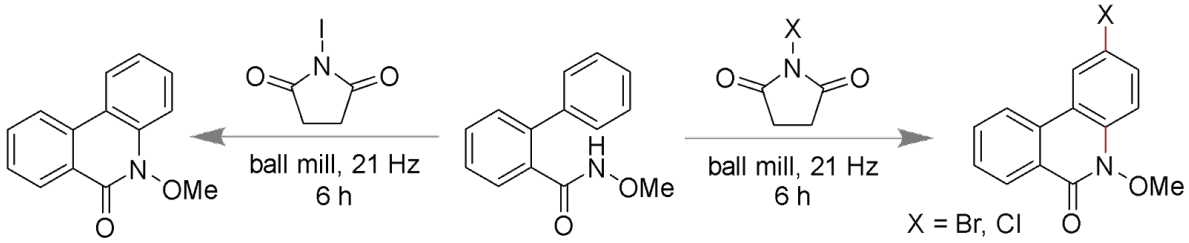
Mechanochemical synthesis offers a robust and sustainable strategy for the construction of N-heterocyclic scaffolds in modern organic synthesis and in addition to the avoidance of the production of 80-90% waste solvent.[1] IUPAC recognized that, Out of ten innovative technologies,[2] mechanochemistry is one of the emerging protocols in chemistry that have the ability to build up our world more sustainable. "Mechanochemistry" is still budding stage and every development utilizing this technique is of utmost importance for a step towards a sustainable world for organic synthesis. Several efforts are going on the invention of "green technologies" for the construction of heterocyclic scaffolds. Phenanthridinone and its analogous are one of the important classes of *N*-containing heterocyclic scaffolds available in many natural products and pharmacologically active compounds.



We have shown herein the use of NBS and NCS as bifunctional reagents for one-pot synthesis of phenanthridinones *via* a cascaded intramolecular oxidative C-N coupling and subsequent halogenation reaction under solvent-free ball milling mechanochemical condition[3].

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P-13

Investigation of the reversible catalytic mechanism of DapF catalyzed epimerization using QM/MM-MD method

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Nowadays, different diseases caused by bacteria are spreading very rapidly in our society. So, we need a large class of active antibacterial drugs to prevent these diseases. Different bacteria metabolize aspartic acid to synthesize amino acids such as lysine, methionine, threonine, and isoleucine, via the 'aspartate pathway'. Among them, L-lysine is a crucial component for bacterial cell-wall biosynthesis. During L-lysine biosynthesis, an essential metabolic intermediate is the meso-diaminopimelic acid (D,L-Dap). In the Gram-negative bacteria Corynebacterium glutamicum (Cg), diaminopimelate epimerase (DapF) enzyme converts the L,L-Dap to D,L-Dap, which is the dominant intermediate of the lysine biosynthetic pathway. The enzyme employs two cysteine residues, one in thiolate form and the other in thiol form, to drive the L,L-Dap to D,L-Dap conversion via deprotonation at one enantiomeric face and further re-protonation from the opposite side of Dap. The development of an inhibitor of this CgDapF enzyme can serve as a novel antibacterial agent. In this presentation, I will discuss our work on the reversibility of the epimerization mechanism by the CgDapF enzyme using the hybrid QM/MM Method coupled with molecular dynamics simulation. The mechanism of action of this enzyme via two different pathways (a single-step mechanism and a two-step mechanism) will be discussed. Various choices for the active site residues in the QM region will be discussed, and their relevance to the overall mechanism of action will be highlighted. The reactant, product, and reactive intermediate will be characterized in terms of their interactions with the protein side chains. The free-energy pathway will be outlined from the weighted histogram analysis of the non-equilibrium umbrella-sampling simulations of the reactive process. Further, I will elaborate my future works on CgDapF to explore more about its mechanistic pathway which is a crucial stage towards designing of novel antibacterial agents.

P-14

Bio-evaluation of Fluoro and Trifluoromethyl Substituted Salicylanil against Multidrug Resistant *S. aureus*

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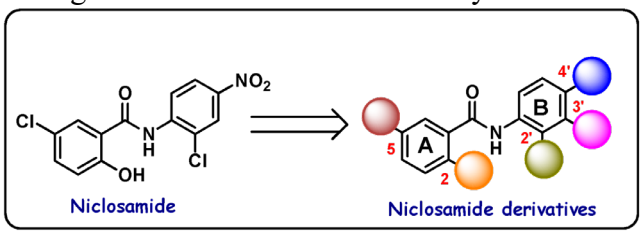
Remdesivir emerged as a boon in the pandemic situation of COVID-19, which proved as a rational example of drug repurposing. Repurposing of the drug (also known as repositioning or rediscovery), gets attention because of its cost-effectiveness and speed up the process due to its pre-established safety and efficacy in Phase I and II clinical trials. One of the key drivers for the repositioning of drugs is the serendipitous discovery of pharmacological activity on new targets, which get supported by the fact that the same molecular pathways may be involved in different diseases. Some classical examples of serendipity-based drug repurposing are thalidomide, sildenafil, and amantadine. In this scenario, our group has selected Niclosamide as a lead compound which is already found to be effective against a variety of human conditions such as cancer and viral infections during drug repurposing screening campaigns. Niclosamide is an FDA-approved anthelmintic drug that has been widely used in humans to treat tapeworm infections. Niclosamide exerts its anticestodal effect by inhibiting oxidative phosphorylation and stimulating adenosine diphosphatase activity in the mitochondria. Being inspired by prominent biological activities of niclosamide our group has synthesized 23 trifluoromethyl salicylanilides derivatives and investigated against the anti-microbial activity.



These compounds inhibited specifically *S.* aureus (MIC 0.25–64 µg/mL). The in vitro cytotoxicity of compounds with MIC < 1 µg/mL against Vero cells led to the identification of four compounds with a selectivity index (SI) above 10. In this screening, 5-chloro-N-(4'-Bromo-3'-trifluoromethylphenyl)-2-hydroxybenzamide **(A)** demonstrated excellent activity against nine MRSA and three VRSA strains with MIC 0.031–0.062 µg/mL, which is significantly better than the control drugs methicillin and vancomycin. The comparative time-kill kinetic experiment revealed that the effect of the bacterial killing of **A** is comparable with vancomycin. SAR data reveals that F at 2'-position, CF3 at 3'-position is important for activity, Br at 4'-position is maintaining the activity, and Cl at 5- and OH at 2-position is responsible for augmenting activity. sOverall, the investigation suggested that the compound could be further developed as a potent anti-staphylococcal therapeutic. These derivatives are also showing anti-viral and anti-cancer activity, and further studies are under progress in our laboratory.

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P-15

Revisiting to β -amyloid fibrillation inhibition based therapeutic strategies for the prevention of Alzheimer's disease

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Protein fibrillation is a self-association phenomenon in which protein molecules with intrinsically disordered, misfolded, or partially unfolded conformations associates in a specific manner to form insoluble higher-order structures. These fibrillar aggregates get deposited in various tissues including the neuronal cell resulting in neurodegenerative disorders like Alzheimer's Disease (AD). The principal component of AD-associated amyloid plaques is a peptide of 35-42 amino acids in length termed as amyloid-β or Aβ peptide. The concept of reduction of Aβ production points to the inhibition of two of its important processing molecules, namely, β- and γ-secretase. However, the primary obstacle in these targets includes the physiological importance of these proteins inside the body that includes differentiation and proliferation of many cell types and the relatively large size of catalytic pocket of the enzyme that demands inhibitors of larger size questions the efficacy and safety of these strategies. This leads to the opening up of ample scope in experimental fields that target direct Aβ clearance because blocking aggregation (while sparing Aβ generation) should not lead to mechanism-based toxicity. Hence, the strategy of inhibiting aggregation of amyloidogenic peptide (Aβ, more specifically the Aβ1-42 isoform) has emerged as a valid disease-modifying therapy. Recently the inhibitory effect of cholic acid (a bile acid) on amyloid fibrillation of insulin has been reported. However, there is a lack of knowledge about how several other bile acids can inhibit the aggregation process of the amyloid-β peptide. Therefore, an attempt has been made to explore the effect of two bile salts (Sodium taurocholatehydrate and Sodium glycolatehydrate) on the fibrillation of Aβ1-42 peptide with the aid of biophysical techniques that include Thioflavin T based fluorescence kinetics assay, circular dichroism etc. The preliminary studies gave a hint towards the inhibitory potential of these two bile salts towards the fibrillation of Aβ1-42 peptide *in vitro*. For future research, this study can be considered as a stepping stone for the development of these bile salts as a potential therapeutic agent against AD without stimulating the immunological responses.

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P-16

Engineered improved siRNA therapeutics against metastatic breast cancer

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RNA interference has huge potential to treat metastatic breast cancer. However, efficient cytosolic delivery of functional siRNA is one of the key challenges for developing effective RNAi therapies. We have engineered multifunctional protease-stabilized facial lipopeptide based siRNA transporters which have demonstrated comparable knockdown efficiency like, HiPerFect, a lipid-based widely-used commercial transfection reagent sold by multinational company, Qiagen. Additionally, unlike HiPerFect, our designed siRNA transporters do not show any toxicity and exhibit very high cytosolic delivery in MDA-MB-231 cells (TNBC) and primary cell line HUVEC (hard-to-transfect cell line), better than HiPerFect. Our designed protease-resistant siRNA transporters also provide stability to siRNA against RNase. Translocation or endosomal escape is an important feature of any efficient siRNA transporter and our *in vitro* data shows endosomal escape of siRNA transporter by pore formation in late endosome mimicking giant unilamellar vesicles.

Notch 1 induces metastasis, proliferation and drug resistance in TNBC and our *in vitro* data demonstrates high level of Notch 1 knockdown by our designed siRNA transporter encased Notch 1 siRNA. Downregulation of metastasis-promoting MMP-2 gene, reversion of epithelial-mesenchymal transition and decreased expression of stemness markers were observed in Notch 1 silenced MDA-MB-231 cells, inferring efficient prevention of cancer metastasis in TNBC. Interestingly, nanobridge-mediated interaction between endothelial cells (HUVEC) and epithelial cells (MDA-MB-231) was also inhibited in Notch-1 silenced MDA-MB-231 cells. In *in vivo* zebrafish model, Notch-1 silenced MDA-MB-231 exhibited prevention of metastasis and cell proliferation. The experimental data demonstrates that our engineered multifunctional siRNA transporters have potential for performing enhanced RNA interference overcoming cancer metastasis. Such siRNA transporters might be translated for developing improved siRNA-based combination therapeutics against metastatic cancer.

P-17

Stereoselective Sulfenylation of Oxindole-derived Propargyl Alcohols to access Sulfenylated-3-Alkenyloxindoles

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We report a Ca-catalyzed, tetrasubstituted alkenyl-sulfenylation using readily available aryl/alkyl thiols and easily prepared oxindole-derived propargyl alcohols under solvent-free conditions.[1] The reaction proceeded with hydrogen bonding assisted regioselective □-thiolation and subsequent calcium catalyzed stereoselective alkenylation to yield *E*-alkenyl thioethers with high diastereoselectivity. The oxindole derivatives, particularly the methylene oxindole moieties, are an integral part of many natural products, they display a broad range of biological activities and hence become challenging targets in medicinal and synthetic chemistry.[2] For example, sunitinib (SU11248) is an orally active receptor tyrosine kinase (RTK) inhibitor marketed by Pfizer as Sutent® which also approved for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumours by the FDA in 2006.[3]

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P-18

Neem leaf extract diminishes the chaperone function of an important small heat shock protein of *Mycobacterium leprae*

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Leprosy is a predominant disease that has afflicted mankind since ancient times affecting the peripheral nerves, causing limb damage and disfiguration of various body parts. In recent times, Southeast Asia shoulders 73% of the world leprosy burden. Since ancient times, Neem has held immense importance in the treatment of leprosy which is well documented in ancient medical treatises such as Charaka Samhita, Sushruta Samhita as well as in more recent Ayurvedic texts of Vagbhatta and Bhavamishra. Different extracts of Neem (leaf, bark, sap) were widely used even in colonial India in the treatment of leprosy[1]. But, the mechanism with which Neem leaf extract helps in reducing the growth and survival of *Mycobacterium leprae* (the causative organism for the disease leprosy) is still far from clear. The non-culturable behavior of *M. leprae* in artificial medium is one of the major causes behind this long standing ambiguity. In spite of this limitation, several efforts have been made to identify the main factors behind the pathogenesis of *M. leprae* inside infected hosts. It has been found that several antigenic proteins contribute to the growth, survivability and virulence of this pathogen. One of them is the 18 kDa antigenic protein[2]. This important immunodominant antigen is a member of the ⟨-crystallin or small heat shock protein family and is also termed as HSP18. Its chaperone function plays a vital role in the growth and survival of *M. leprae* pathogen[3]. However, the effect of Neem leaf extract on its structure and chaperone function is still unclear. Therefore, we have taken a thorough attempt to understand the possibility of interaction between HSP18 and Neem leaf extract (methanolic) using biophysical techniques. We observed from our study that methanolic Neem leaf extract (harbouring significantly flavonoids and phenolic compounds) efficiently interacts with HSP18. Such interaction alters the secondary structure and tertiary structure of HSP18 as well as greatly reduces its surface hydrophobicity. All these structural alterations together eventually reduces the chaperone function of HSP18.

The reduction of chaperone function of this important antigenic protein in presence of Neem leaf extract may possibly play a significant role in controlling the growth and survival of *M. leprae* pathogen in infected hosts. Additionally, this study opens up the possibility of usage of various phytochemicals (especially flavonoids and phenolic compounds) for the effective treatment of leprosy.

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P-19

Molecular Editing of Proline Rich Antimicrobial Peptides.

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The burden of infectious diseases in India remains extremely high and lower respiratory infections, diarrhoeal diseases and tuberculosis are among the ten deadliest diseases. Despite the presence of many small molecular and peptide antibiotics, untreatable infectious diseases are increasing rapidly due to acquiring antibiotic resistance by pathogenic microbes to antibiotics. At present, only two new peptides antibiotics called murepavdin and NXL103 are in the advanced clinical stage for treating drug resistant gram negative bacterial infection. A joint initiative of WHO and GARDP encourages public-private partnership to develop and deliver four new treatments by 2023, through improvement of existing antibiotics and acceleration of the entry of new antibiotic drugs. Given the importance of developing potential peptide antibiotics and inspiring by potency and druggable features of gramicidin S, we edited proline α-carbon with a nitrogen and seen the direct impact on biological activity with respected to prolyl peptide counterpart. The proline edited gramicin S mimics **1** and **2** (Figure-1) represented twofold better active and biostable than the natural gramicidin S. Unlike the conventional peptide drug discovery, the molecular editing of antimicrobial peptides provides an opportunity to access wide variety of derivatives, without perturbing core peptide scaffold. The biological results demonstrate that constraining proline α-carbon with a nitrogen in a prolyl antibiotics provide rigidity, resist proteolytic degradation and improve pharmacokinetic properties.

Figure 1: Molecular editing proline α-carbon with a nitrogen and their antimicrobial activity.

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P-20

Rationally designed peptide-based cancer nanotherapeutics

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Harnessing self-assembled peptides for generating nanostructured material possess a great promise in delivering toxic conventional small molecule drugs and nucleic acid-based biopharmaceuticals for developing cancer nanotherapeutics. Clinically safe intracellular delivery of cargo in functional form remains a major concern for the pharmaceutical industries. We aim to engineer peptide-based therapeutics for intracellular functional drug delivery and developing combination therapy for breast cancer treatment. We have evaluated gramicidin (gA) and gA-inspired hydrophobic peptide (LD8) for delivering doxorubicin (Dox) and TAT-peptide inspired arginine-rich cell penetrating peptides for intracellular delivery of functional siRNA to silence critical oncogenic pathways. Both gA and LD8 induce cytotoxicity, mitochondrial depolarization and apoptosis against MDA-MB-231. Doxorubicin loaded LD8 (LD8-Dox-NP) and doxorubicin loaded gA (gA-Dox-NP) showed cytotoxicity and apoptosis, evidenced by DNA fragmentation and Western blot analysis of PARP cleavage and upregulated tumor suppressor protein p53, that inhibits cell proliferation. gA-Dox-NP and LD8-Dox-NP induce S and G2 phase cell cycle arrest, respectively, indicating inhibition of DNA synthesis by gA-Dox-NP and DNA damage in presence of LD8-Dox-NP. gA-Dox-NP and LD8-Dox-NP can be potentially used as 2-in-1 nanomedicine in treating breast cancer. Our designed arginine-rich molecular transporters demonstrated functional siRNA delivery in MDA-MB-231 cell line like commercial transfection agent HiPerFect and showed significant gene silencing in upregulated MAPK/ERK signaling pathway in breast cancer, evidenced by RT-PCR and immunofluorescence studies. We are also examining these against pathways upregulated in drug resistance, metastasis and epithelial-mesenchymal transition. We anticipate such therapeutic peptides might be translated to clinics for developing advanced siRNA based nanotherapeutics, combination therapy in breast cancer treatment and silencing signal transduction of oncogenic pathways can emerge as unique paradigm in developing cancer nanomedicine.

P-21

Apixaban analogues from ethyl 2-chloro-2-(2-(4-methoxyphenyl) hydrazineylidene) acetate

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The 1,3-dipolar cycloaddition[] (DC) reaction of substituted acenaphthenone-2-ylidine ketone with nitrile imines[] generates the corresponding dihydro-2*H*-spiro [acenaphthylene-1,3'-pyrazole] cycloadducts in very good yields (up to 92%) with high regioselectivity. A reaction was performed between ethyl (*Z*)-2-chloro-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (**1**) and (*E*)-2-(2-([1,1'-biphenyl]-4-yl)-2-oxoethylidene)acenaphthylen-1(2H)-one (**2**) with optimized conditions. This smooth conversion gave ethyl (1R,4'R)-4'-([1,1'-biphenyl]-4-carbonyl)-2'-(4-methoxyphenyl)-2-oxo-2',4'-dihydro-2H-spiro [acenaphthylene-1,3'-pyrazole]-5'-carboxylate (**3**) in 87% yield. The structure and regiochemistry were determined by spectroscopic data and single-crystal X-ray diffraction analysis.

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P-22

Pyrediyne quantum dots from two-dimensional pyrediyne nanosheets for bioimaging of cancer cells

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Preparation of 0D quantum dots from their 2D analogues is desirable to explore their exciting luminescent properties and enhance their applications in various biological and optoelectronic devices. Carbon based quantum dots are widely acclaimed for their non-toxic properties. A carbon based 2D material known as pyrediyne,[1] which is a new addition to the graphdiyne family, was designed and synthesized and 0D pyrediyne quantum dots were extracted during the preparation of the 2D materials. A simple and cost-effective soxhlet extraction method as well as ultrasonication method were employed for the preparation of the quantum dots.[2] Average size and morphology of the as-prepared quantum dots were obtained as <10 nm by high-resolution transmission electron microscopy (HRTEM) and the lattice fringes visible in the image provided insights about the semi-crystalline nature of the synthesized quantum dots, similar to their 2D counterparts. Absence of sharp peaks in X-Ray Diffraction (XRD) pattern further confirmed their semi-crystalline nature. As-prepared quantum dots were further characterized by transmission electron microscopy (TEM), atomic force microscopy (AFM) and matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS). Presence of oxygen-containing groups in prepared quantum dots was confirmed via Fourier-transform infrared spectroscopy (FTIR). Photophysical properties of pyrediyne quantum dots were studied using UV-Visible spectroscopy, fluorescence spectroscopy and time correlated single photon count (TCSPC). Easy and cost-effective preparation methods as well as properties like non-toxic nature, absence of transition metal contents, and better photoluminescence quantum yield (~23%) made these quantum dots unique for biomedical applications, compared with the existing inorganic and carbon-based quantum dots. Following cell viability analysis, pyrediyne quantum dots were utilized for bioimaging of MCF7 breast cancer cells.[2] The details of the synthesis, characterization and application will be presented in the poster.

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P-23

Cyclization/Annulation Reactions from *In situ* Generated Homoallenyl ketones

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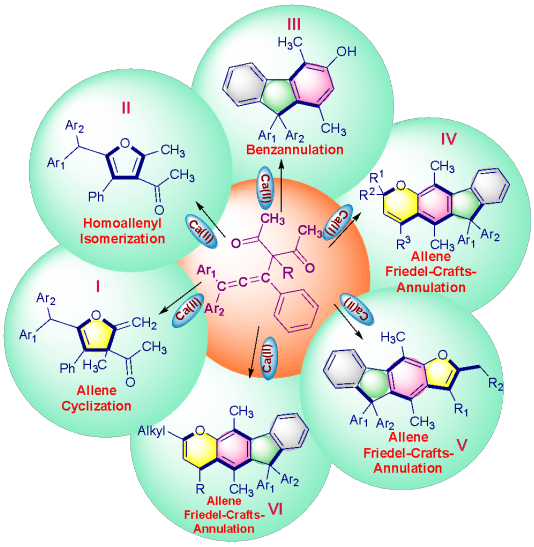
A facile synthesis of dihydrofurans bearing a quaternary centre[1] through 5-*end-dig* cyclization when the diketo center of allene is tertiary, homo-allenyl ketone undergo isomerization followed by 5-exo-trig cyclization to tetrasubstituted furan[1], fluorenols[2] were formed by allene Friedel-Craft annulation, etherification of flurenol with *tert*-propargyl alcohol and 3,3 rearrangement resulted to tetracyclic fluorenopyrans[3], whereas alkylation with *sec*-propargyl alcohol followed by 5-*exo-dig* cyclization gave tetracyclic fluorenofurans in case of sec-propargyl alcohols bearing an alkyl group on the alkyne-terminus resulted fluorenopyran from simple acyclic reactants, propargyl alcohols and 3-methyl pentane-2,4-dione under calcium catalysis. This one-pot reaction proceeds through homoallenyl ketone which is formed *via* S_N2' mechanism. These synthesized products are important in chemical biology and material science and also show similarity with some natural products. For example, fluorenopyran represent an important class of heterocyclic compounds from both pharmaceutical and biological point of view. Compounds comprising the furan or tetrasubstusted furan ring are biologically active and are existent in a number of pharmaceutical products.



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P-24

Network Pharmacology of *Mycobacterium tuberculosis* H37Rv proteins and interacting phytochemicals

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Pulmonary tuberculosis caused by *Mycobacterium tuberculosis* have a staggering global impact on public health. The long-term treatment regimen and ability of organism to acquire drug-resistance calls for rapid discovery of new and active compounds to inhibit the organism. In this regard, phytochemicals from traditional medicinal plant have proven to be a good source of bio-active compounds. One such plant is *Acacia nilotica,* which has shown wide spectrum of bioactivity against respiratory diseases, (2). Our preliminary results also demonstrated that hexane-methanolic extract of *A.nilotica* exhibits antibacterial activity against *M. smegmatis* (non-pathogenic model for *M. tuberculosis*) (1). The present study undertook a network pharmacology based approach, in order to identify the potential anti-mycobacterial phytochemical from *A.nilotica* and also to predict its possible mechanism of action.

A protein-protein interaction (PPI) network was constructed for *Mtb* proteins using Cytoscape and STRING interactions server. The network was then clustered and ranked using MCODE algorithm and thereby the final network consisting of 9 clusters, with 395 nodes and 4656 edges. The PPI network was analyzed based on degree, eigenvector centrality, betweenness centrality to identify the central proteins which were important in individual cluster and also in overall network. The phytochemicals from *Acacia nilotica* were docked with the cluster proteins using PyRx version 0.8 (AutoDock-Vina). A protein-phytochemical network was constructed for each cluster based on their docking binding energy and the effect of phytochemical has been evaluated based on the topological parameters of network including degree, centrality, and cluster co-efficient. To validate the constructed network and the workflow, the effect, and interactions of commercial drugs namely, rifampicin, Isoniazid and Dapsone has been studied comparing with their literature reported interaction. The network analysis of phytochemicals of *A.*nilotica suggested 15 potential phytochemicals to exhibit anti-mycobacterial activity, notable, Betulin, Pyrogallol and Ellagic Acid were found to have significant interactions with the PPI network. This study culminated in a better understanding of the mechanisms of anti-microbial action of *Acacia nilotica* phytochemicals on *Mycobacterium tuberculosis* as well as to propose bio-active lead candidates for designing anti-mycobacterial inhibitors

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P-25

Spirooxindole pyrrolidinyl derivatives: Synthesis, Characterization, Molecular docking and Anti-diabetic activity studies

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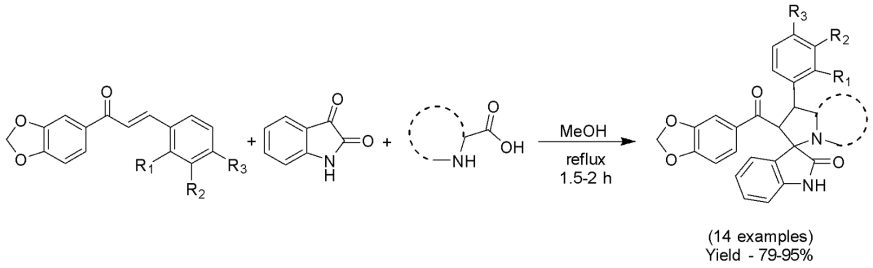
Spirooxindoles are promising pharmacological agents that are present in multitudinous natural products and biologically active molecules. Significantly, pyrrolidinyl spirooxindole cores have been found in several numbers of natural products, such as alstonisine, pteropodine, formosanine, spirotryprostatin A and medicinally important NITD 609.The spiropyrrolidinyl oxindoles were utilized as a promising synthetic intermediate and exhibited good biological activities, including anti-diabetic, antifungal, anti-inflammatory, anti-tumor, anti-tubercular, anti-malarial, acetylcholinesterase (AChE), antiviral inhibition properties. The presence of the oxindole core and other heterocyclic moieties (usually fused at the C-3 position of the oxindole) together makes these motifs an interesting target for drug discovery. The azomethine ylide chemistry has achieved significancein modern years as it provides as an essential route for theassembly of nitrogen containing five membered heterocycles. Herein we present the synthesis involves the 1,3-dipolar cycloaddition reaction of benzodioxole chalcones (dipolarophiles) with azomethine ylide (dipole) which is a reactive intermediate generated *in situ* by the decarboxylative condensation reaction between amino acid and 1,2-dicarbonyl compounds



Scheme-1 Synthesis of Spiro-pyrrolidinyl derivatives

The desired products were well characterized by FT-IR, ^{1}H and ^{13}C NMR, HR-MS spectral analysis and further confirmed by X-ray diffraction studies. Further, the *in-vitro* anti-diabetic activity of synthesized compounds against α-amylase and α-glucosidase enzymes, which showed that compounds exhibited excellent inhibitory activity will be discussed in the conference.

P-26

Naturally Derived Novel Drug Candidates against Microbial Virulence: Synergistic Combination of Malabaricone B and Gentamycin Efficiently Targeting the MDR *S. aureus* Infections

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Antibacterial agents that have potent activity against MDR strains are of enormous interest. Bacterial resistance over the existing drugs has become the most challenging issue in curing the infections caused by various pathogens. Over consumption and rampant use of antibiotics resulted the development bacterial resistance over it [1]. Bacteria became more adaptable to antibiotics and they have improved their ability to defeat the drugs designed to kill them. Continuous exposures to the commonly existing antibiotics make them evolve resistance over it and which in turn reduces the effectiveness of the drug to manage the infectious diseases. In this context, limitations of the existing antibiotics highlight the critical need for novel antibacterial agents capable of competing against the bacterial resistance and to improve the effectiveness of the therapy. Our approach is mainly focused on the effective utilization of naturally abundant secondary metabolites for the development of potent antibacterial drug leads. Since various biological activities possessed by the polyphenolic compounds are impressive, we have utilized the phenyl acyl phenol class of compounds from the myristicaceae family for the detailed *in vitro* and *in vivo* antibacterial screening. In this presentation we will discuss in detail the antibacterial efficacy studies of malabaricones (the unusual class of phenylacyl phenols) against *S. aureus* including MDR strains along with its synergistic combination studies with the existing antibiotics for targeting the MDR-*S. aureus* infections [2].

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P-27

Catalytic δ-Hydroxyalkynone Rearrangement in the Stereoselective Total Synthesis of Centrolobine, Engelheptanoxides A and C, Obolactones and 7',8'-Dihydroobolactones

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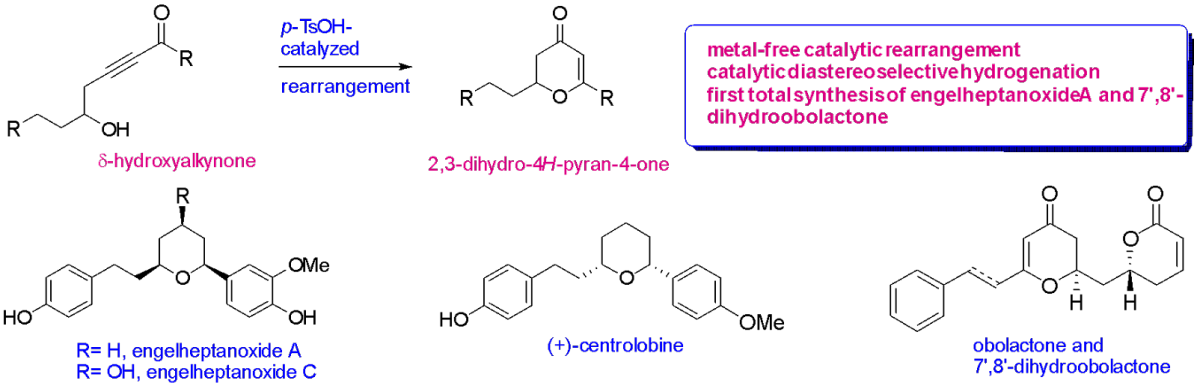
A unique metal free *p*-TsOH catalyzed rearrangement of □-hydroxy-alkynones to 2,3-dihydropyran-4-ones has been employed to the synthesis of biologically active natural products.[1] A catalytic stereoselective total synthesis of centrolobine and engelheptanoxides A & C has been completed via a metal-free catalytic □-hydroxyalkynone rearrangement to 2,3-dihydro-4*H*-pyran-4-one and diastereoselective hydrogenation to the all *syn*-2,4,6-trisubstituted pyran strategy.[2] The onliest required chirality was introduced by Jacobsen kinetic resolution, which further directed the diastereoselective hydrogenation. The analogues and derivatives of centrolobine and engelheptanoxides prepared were evaluated for antitubercular activity against *M. tuberculosis* H_{37}Rv ATCC 27294. And also a concise stereoselective total synthesis of two diastereomeric obolactones and 7′,8′-dihydroobolactones has been achieved employing a metal-free catalytic □-hydroxyalkynone rearrangement, which could set the required dihydro-□-pyrone moiety.[3] The desired first stereogenic center has been installed through the chiral pool material, L-aspartic acid. Next, the allylation reaction was strategically utilized to provide the requisite olefin bond for the intended ring-closing metathesis allowing the installation of remaining dihydro-□-pyrone moiety in the natural products. It also enabled targeting both dihydro-□-pyrone diastereomers. Thus, the first stereoselective total synthesis of (+)-7′,8′-dihydroobolactone and engelheptanoxide A was accomplished establishing their structure and absolute configuration.



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P-28

Disulfide Metathesis *via* Sulfur…Iodine Interaction and Photoswitchability

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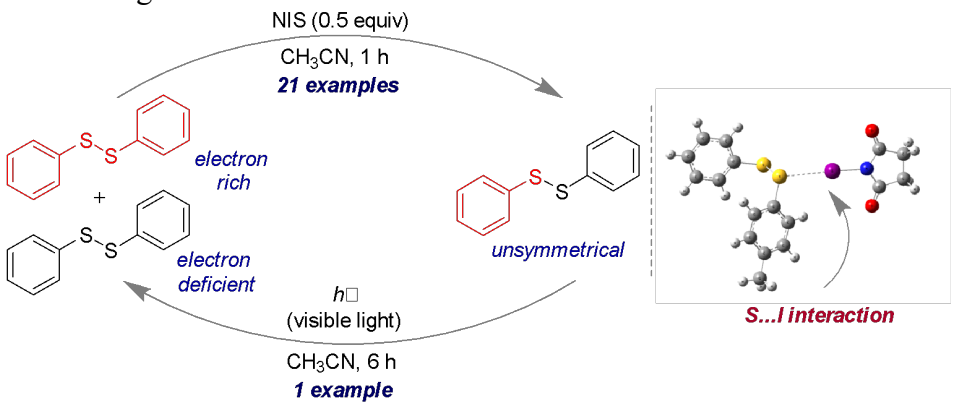
In recent years, S-S bond formation reactions have gained popularity in synthetic organic chemistry. Indeed, the synthesis of unsymmetrical diaryl disulfides is challenging due to the presence of a weak S-S bond. The disulfide bond is one of the most important structural functionalities which plays a crucial role affecting the stability, folding, and biological function of proteins and peptides. The synthesis of unsymmetrical disulfides is an important step for the preparation of a variety of compounds involved in medicinal chemistry. We report herein the synthesis of unsymmetrical diaryl disulfides from two symmetrical disulfides *via* a cross-metathesis reaction which was controlled by a weak sulfur…iodine (S…I) interaction. The unsymmetrical disulfides were stable in acetonitrile solution in the presence of *N*-iodosuccinimide (NIS), and found to be photoswitachable reversibly to the symmetrical disulfides under visible light irradiation.



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P-29

Engineered Bio-inspired Peptide Based Total Wound Care

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Engineering nature-inspired peptide-based "Total Wound Care" in treating bleeding disorder followed by wound healing via therapeutic angiogenesis holds great promise in designing next-generation regenerative medicine. Uncontrolled bleeding is major cause of death of accident victims, injured soldiers and patients having inherent bleeding disorders. Additionally, non-healing diabetic wound causes significant healthcare problems often leading to pain, suffering and poor life quality of patients. None of the current hemostatic agents or nanomedicines simultaneously offers advantage of blood clotting and accelerated wound healing. To address the issues of impaired blood clotting and diabetic wound healing, there is urgent need to develop biocompatible "total wound care". Growth factor mimetic peptide-based functional biomaterials are promising ingredients for engineering improved proangiogenic therapy. In our study, we have evaluated combination of our designed isopeptide-bond stabilized peptide-based sealant and VEGF mimetic peptide QK for "total wound care". Interestingly, MD simulation studies reveal that unlike natural VEGF15 ligand, peptide QK retains its helical conformation, which is essential for its biological function like full length biologically active VEGF ligand. Peptide QK co-administered with peptide-based sealant exhibit accelerated wound healing in *in vivo* rabbit model by promoting therapeutic angiogenesis. Histopathological studies reveal that this wound care material has exhibited mature and compact extracellular matrix fiber deposition at wounded site compared to control wounds, as evidenced by staining of collagen, elastic and reticulum fibers. Such nature-inspired peptide-based nanomedicine has immense potential to be translated into clinics as biocompatible total wound care.

P-30

Nitrative and chlorinative cyclization of aryl alkynoates: Access to 3-nitro coumarins and 3-chloro coumarins

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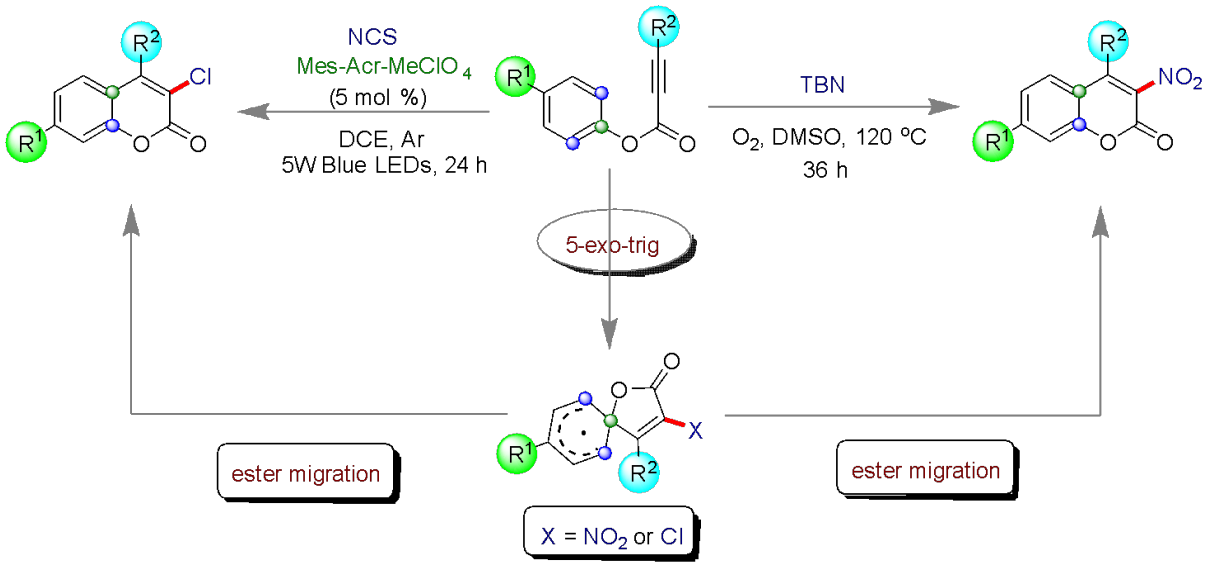
Coumarin framework is one of the important structural scaffolds widespread in bioactive molecules and natural products. Because of biological and pharmaceutical importance of these privileged heterocycles, synthesis of 3-functionalized coumarins via radical cascade cyclization reactions of aryl alkynoates have been an important topic to synthetic organic chemists. Here the first approach portrays the synthesis of 3-nitro coumarins[1] via *tert*-Butyl Nitrite (TBN) medited nitrative cyclization of aryl alkynoates. Parallelly, in the second approach synthesis of 3-chlorocoumarins[2] has been achieved via chlorinative cyclization of aryl alkynoates, using *N*-chlorosuccinimide (NCS) as chlorine source and Mes-Acr-$MeClO_4$ as a visible-light photocatalyst. In both protocols, the reaction proceeded through 5-exo-trig spirocyclization and subsequent 1,2-ester migration. High regioselectivity, good functional group tolerance, use of metal-free reagents are the key advantages of these sustainable protocols.



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P-31

Oxanorbornane-based synthetic lipids as vehicles for anticancer drugs: Insights into uptake mechanism and cellular distribution

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Development of safer and effective drug delivery systems (DDSs) is an active area of research and is a reliable strategy to address ADMET-related issues. Though a large number of DDSs have been studied in the last several decades, their clinical development is still challenging as they need to meet several requirements during *in vivo* application. Lipids, polymers and metal-organic frameworks are amongst the important types of chemical systems studied in this regard. Since synthetic chemistry allows design of lipids with different polarity and assembly characteristics, we are involved in the development of a new class of lipids based on hydroxylated oxanorbornane-based head group. As part of these efforts, we have designed and accessed a new analog with NBD tag on the head group, and have investigated its uptake and distribution in A549 cells. Solid-lipid nanoparticles (SLPs) and vesicles of this lipid in a co-assembled state with phosphatidyl choline and cholesterol were prepared and characterized by DLS, AFM and TEM techniques. Aggregates of this NBD-conjugate were found to get distributed predominantly in the cytosolic side, and to a lesser extent in the nucleus, as per confocal microscopic analysis. Detailed experiments to understand the uptake mechanisms indicated operation of both passive and caveolae-mediated endocytic pathways. Ability of this class of lipids to entrap doxorubicin and release it in a sustained manner was also verified through *in vitro* experiments. Biocompatibility studies ensured that the synthesized lipid can be employed as effective agents for intracellular drug delivery.

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P-32

Purine-modification as a strategy to improve the antimalarial potency of quinolones

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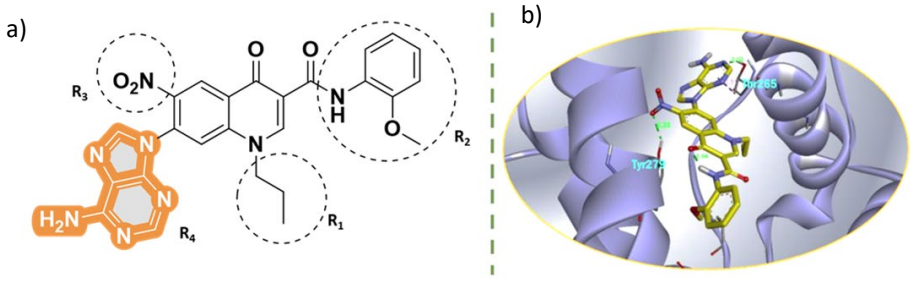
Quinolones are well known in the area of antibacterial chemotherapy and are also receiving considerable attention as promising leads against malaria parasite. Their mode of action against the latter involves interference with the function of cytochrome bc1 complex that is part of the mitochondrial electron transport chain. Though a large number of quinolones have been investigated for antimalarial chemotherapy, their clinical development was not very successful. Poor aqueous solubility and poor *in vivo* efficacies were the problems with many of these derivatives.[1-3] In this context, new approaches to improve their physicochemical properties and *in vivo* efficacy is of considerable interest. As part of our interest in this area, we have been investigating the biological activities of a library of adenine-modified quinolones. During these studies, a noticeable improvement in their antimalarial potency was observed on introduction of adenine at C-7 position. Modelling studies showed that adenine not only contributes to target binding but also significantly improves the physicochemical properties of this class of compounds.[4] These aspects will be elaborated during this presentation.



- *Adenine modification improves the potency as well as physicochemical properties*
- *Leads to mitochondrial disfunctions*
- *Adenine unit contributes to target binding (Q_o site of cyt. bc1 complex)*

Figure 1. a) Adenine-modified quinolones with different array of substituents at N-1, C-3 and C-6 positions. b) binding of the most active compound in the Q_o site of cytochrome bc1 complex.

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Sulfur-Centered Weak Interactions in C-S Bond Formation Reactions

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Sulfur centered weak interactions are mainly explored to design many drug molecules and to stabilize the tertiary structure of proteins[1, 2]. Not only this, weak interactions or non-covalent interactions can also play pivotal role to derive many chemical processes *via* weakening strong covalent bonds. Again, controlling regio and stereo-selectivity in a hydrothiolation reaction is always challenging. This presentation highlights how sulfur-centered weak interactions like S-H...π interaction, N-H...S Hydrogen bonding interaction and S...O interaction could act as driving force of the thiol yne click (TYC) reactions to attain exclusive control on selectivity (Figure 1)[3-7].

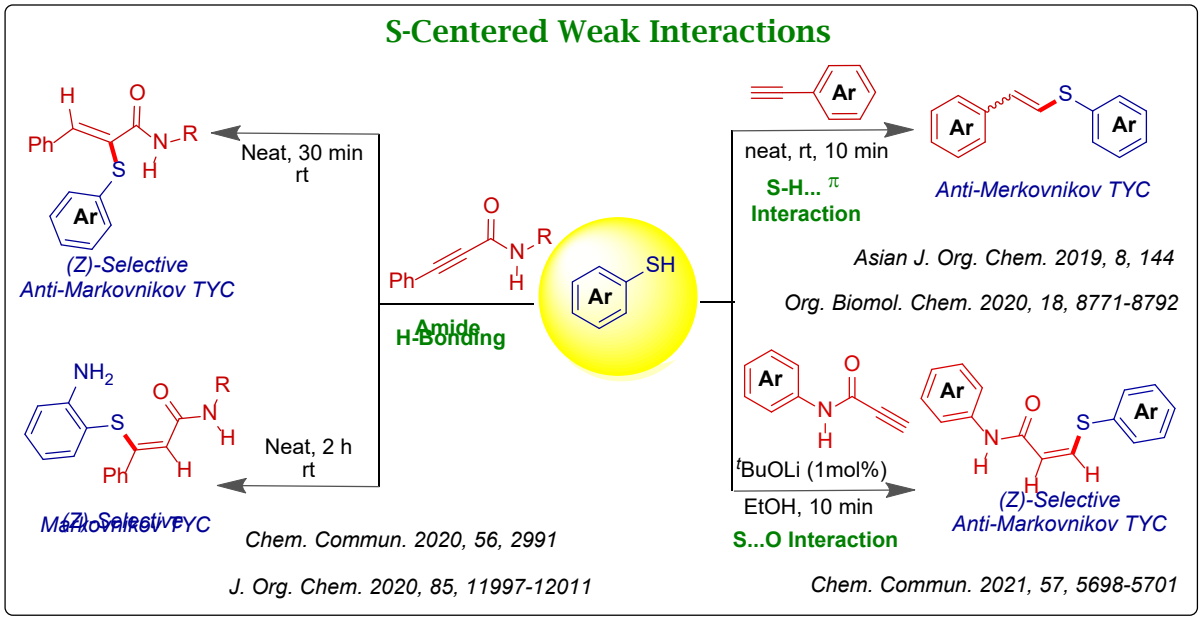

Figure 1. Weak Interaction Controlled C-S Hydrothiolation Reactions.

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