Dr. Arindam Talukdar (Nomination No: 2023/RA-95)

Senior Principal Scientist, CSIR-Indian Institute of Chemical Biology, Kolkata

Ten Papers: Briefly highlighting the contributions in them

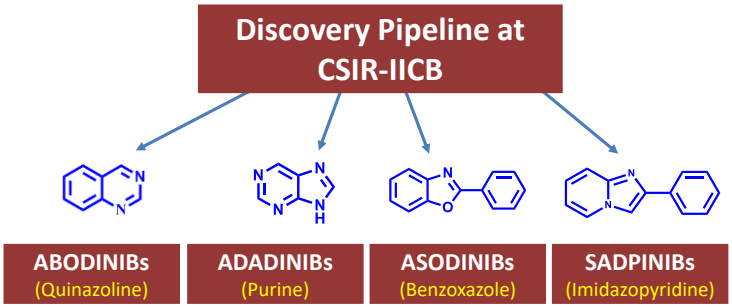
HIGHLIGHTS OF CONTRIBUTIONS TO THE AREA OF SPECIALIZATION

I have an interdisciplinary background with a Master's degree in Pharmaceutical Chemistry from Panjab University Chandigarh and Ph.D degree in Chemistry from CSIR-National Chemical Laboratory (NCL), Pune. My Ph.D. research was an amalgamation of fundamental discovery followed by industrial applications. **The industrial project was funded by CytoMed, USA/Millennium Pharmaceuticals USA** towards stereoselective development of a drug candidate CMI-977 and its analogues. CMI-977 completed the Phase 2 clinical trial. *The key methodology that was developed was extended for the commercial manufacturing of stereoselective β-blocker drugs in the Indian industry*. I spent six years in the USA as a postdoctoral fellow at The Ohio State University and Purdue University, where I obtained training in glycobiology, glycochemistry, and various aspects of Chemical Biology and Medicinal chemistry related to drug discovery. Thereafter, I had a very impactful industrial stint for two-and-half years working as a Senior Research Scientist at Albany Molecular Research Inc, Singapore. As a team leader, I was instrumental in developing and validating first-in-class epigenetic target small molecules from high-throughput screening into the pre-clinical stage. The industry awarded me with inventorship. I joined CSIR-Indian Institute of Chemical Biology (IICB) in January 2013 as a Senior Scientist. Recently I have been promoted to Senior Principal Scientist with merit. The following are the major outputs/outcomes of our research group:

i. Advancement of the fundamental concept of medicinal chemistry drug discovery.
ii. Seminal contribution to the field of medicinal chemistry in general.
iii. Empowering and training PhD and Master's students in drug discovery concepts and strategies, which will foresee the advancement of Indian drug discovery research in coming years.
iv. Providing a conceptual drug discovery model for the medicinal chemistry community for the future generation of the potential drug candidate.
v. Conducting workshops on medicinal chemistry concepts for students (I have conducted four such workshops with international speakers and hands-on training for students across India free of any charges).
vi. Publishing our work in high-impact journals for recognition of Indian Medicinal Chemistry research.
vii. Patenting our work for possible commercialization.

The main contribution towards the Discovery and Development of dual TLR7 and TLR9 Antagonists for autoimmune diseases at CSIR-IICB. The human innate immune system is the first line of defense against the invasion of pathogenic microorganisms. Toll-like receptors (TLRs), mostly expressed on antigen-presenting cells such as dendritic cells, are germline-encoded pattern recognition molecules that play key roles in innate immunity by regulating inflammation. Among the family of TLRs, TLR3, TLR7, TLR8, and TLR9 have been identified in humans that are located inside the endosomal compartments (pH = 4.5−6.5) of the immune cells and they recognize nucleic acids of both pathogenic

origin and self-origin. Aberrantly activation of endosomal TLR7/8/9, initiates autoreactive inflammation in different autoimmune diseases such as systemic lupus erythematosus (SLE), psoriasis, Sjögren's syndrome and systemic sclerosis. The role of TLR7/9 is well established and can serve as an ideal therapeutic target for novel drug discovery, leading to the amelioration of these diseases. The lab is involved in conceptualizing, rationally designing, developing, and validating dual and selective antagonists for the nucleic acid-recognizing TLRs (TLR7 and TLR9) for devising novel therapeutic strategies in relevant clinical contexts. An exhaustive pipeline consisting of molecules from Purine, Quinazoline and Imidazopyridines. **IICB has initiated talk and held multiple meetings with the executives from with Sun Pharmaceutical Industries and Zydus Lifesciences for licensing out the technologies for the approved patented work.**



Till now the work resulted in two GRANTED patents (WO/2019/092739- US20200347062B2-**Granted** Date: 09.11.2021; WO2017/163264A1- US10662177B2 **Granted** Date: 26.05.2020) and many publications in reputed medicinal chemistry journals.

Advanced-level talk is ongoing with Pharmaceutical industries for licensing out these patented CSIR technologies. The RC members appreciated the success of the project.

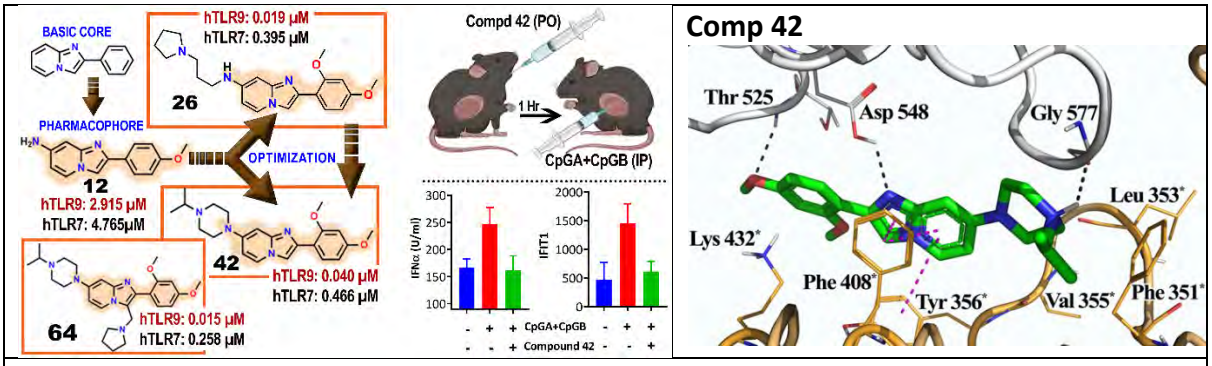
DIFFERENT STRATEGIES ARE EMPLOYED FOR DRUG DISCOVERY.

<u>TEN PAPERS HIGHLIGHTING CONCEPTUALIZATION AND DRUG DISCOVERY STRATEGIES ARE:</u>

1) Strategic Development of New Chemotypes
2) Conceptual development of antagonists from agonist structure through single-point change
3) Lead Optimization Strategy
4) Activity-Based Design and Development
5) Design facilitated by Universal Binding model and ligan-receptor interactions analysis.
6) Optimization of Existing Scaffolds
7) Medicinal Chemistry Strategy to Mitigate hERG Liability.
8) Fragment-Based Drug Design Strategy
9) Hypothesis-driven tailor-made Topoisomerase 1 Poison
10) Editorial, Perspectives, and Review Articles for the Medicinal Research Community.

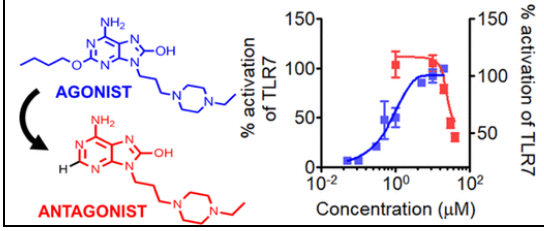
DIFFERENT STRATEGIES ARE EMPLOYED FOR DRUG DISCOVERY.

1) ***Strategic Development of New Chemotypes***. High-throughput screening to identify new chemotypes is often out of the reach of academics. We report a drug development strategy to identify a new chemotype based on the strategy to establish minimal pharmacophoric features on the core followed by hit-to-lead optimization, guided by ligand−receptor binding hypothesis, in vitro and in vivo biological assays and ADME. Our strategy is to develop a new chemotype "imidazopyridine" as dual TLR7/TLR9 antagonists from the basic molecular framework and deducing the chemical spaces through sequentially incorporating relevant structural subunits to identify minimal pharmacophoric features, thereby sculpting the SAR *(**Journal of Medicinal Chemistry***, **2022**, *65*, 11607).



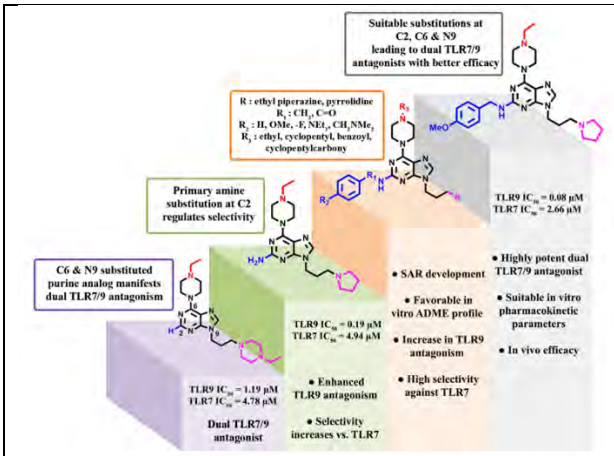
Development, Optimization, and In Vivo Validation of New Imidazopyridine Chemotypes as Dual TLR7/TLR9 Antagonists through Activity-Directed Sequential Incorporation of Relevant Structural Subunits. Das N, Bandopadhyay P, Roy S, Sinha BP, Dastidar, UG, Rehman O, pal S, Ganguly D,* & **Talukdar A** ***. *Journal of Medicinal Chemistry*, **2022,** 65, 17, 11607. https://doi.org/10.1021/acs.jmedchem.2c00386

2) ***Switching Agonist to Antagonist in Purine Scaffold***. Purine scaffold is known for depicting TLR7/9 agonism. We report the purine scaffold as TLR7 antagonist, a first-of-its-kind. We hypothesize that both agonist and antagonist of TLR7 bind at a similar site thus, might share similar chemical-structural features for receptor affinity. We mapped the path for transforming agonist to antagonist through **a single-point** '***Chemical Switch***' in TLR7 ligands that can reverse their functional activity. *The removal of the butoxy group at C2 position of the TLR7 purine agonist transforms the TLR7 agonist into TLR7 antagonist.* To further validate the in vivo applicability of this novel TLR7 antagonist, we demonstrated its excellent efficacy in preventing TLR7-induced pathology in a preclinical murine model of psoriasis. (***Journal of Medicinal Chemistry***, **2020**, *63*, 4776).



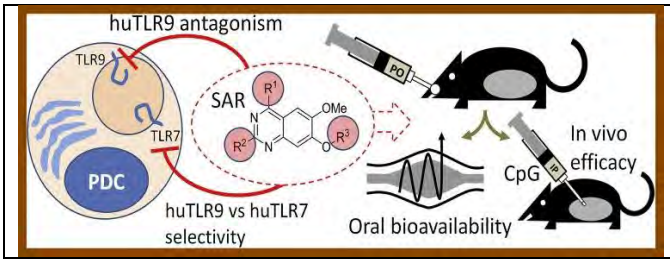
A Chemical Switch for Transforming a Purine Agonist for Toll-like Receptor 7 to a Clinically Relevant Antagonist. Mukherjee A, Raychaudhuri D, Sinha BP, Kundu B, Mitra M, Paul B, Bandopadhyay P, Ganguly D,* and **Talukdar A*.** ***Journal of Medicinal Chemistry***, **2020**, 63, 4776. https://doi.org/10.1021/acs.jmedchem.0c00011.

3) ***Lead Optimization Toward Dual TLR7/TLR9 Antagonists***. We illustrate here the importance of C2, C6, and N9 substitutions in the purine scaffold for antagonism to TLR7 and TLR9 through structure−activity relationship studies using cellular reporter assays and functional studies on primary human immune cells. The lead validation through systematically optimizing via in-vitro DMPK, in-vivo pharmacokinetics, in-vitro and in-vivo toxicity assessment, in-house pharmacodynamic mouse model was done. Isothermal titration calorimetry excluded direct TLR ligand−antagonist interactions. In vivo antagonism efficacy against mouse TLR9 and therapeutic efficacy in a preclinical murine model of psoriasis highlighted the potential of the lead candidate as a therapeutic candidate in relevant autoimmune contexts. (***Journal of Medicinal Chemistry***, **2021**, 64, 9279).



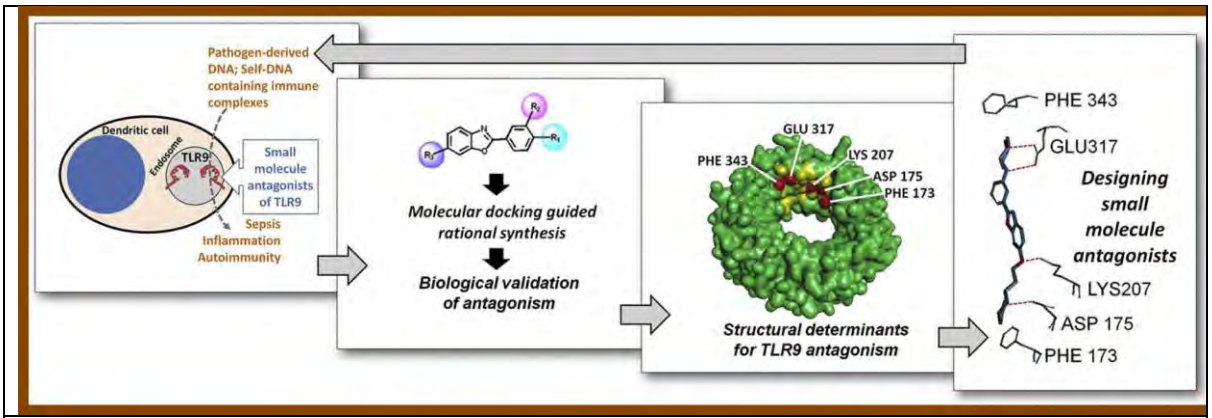
Systematic Optimization of Potent and Orally Bioavailable Purine Scaffold as a Dual Inhibitor of Toll-Like Receptors 7 and 9. Kundu B, Raychaudhuri D, Mukherjee A, Sinha BP, Sarkar D, Bandopadhyay P, Pal S, Das N, Dey D, Ramarao K, Nagireddy K, Ganguly D,* and **Talukdar A***. ***Journal of Medicinal Chemistry*, 2021,** *64*, 9279. https://doi.org/10.1021/acs.jmedchem.1c00532.

4) Activity Guided Rational Design from Quinazoline Scaffold. Through an activity-guided approach, we have identified chemical features in orally bioavailable quinazoline core that are essential for selective hTLR9 inhibition as well as dual TLR7 and TLR9 inhibition. We elucidate the importance of specific physiochemical properties through substitution patterns in quinazoline scaffold to achieve potent hTLR9 inhibition at < 50 nM as well as > 600-fold selectivity against hTLR7, (***European Journal of Medicinal Chemistry*, 2018**, 159, 187).



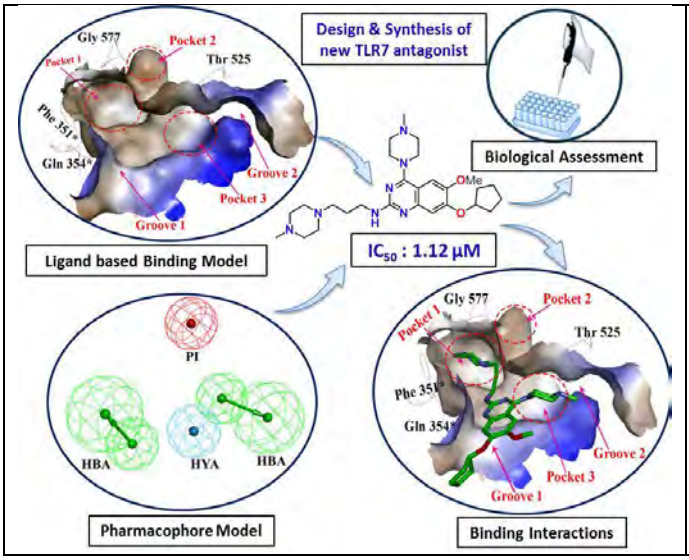
Activity-guided Development of Potent and Selective Toll-like Receptor 9 Antagonists. aul B, Rahaman O, Roy S, Pal S, Satish S, Mukherjee A, Ghosh AR, Raychaudhuri D, Bhattacharya R, Goon S, Ganguly D*, **Talukdar A***. ***European Journal of Medicinal Chemistry*, 2018**, 159, 187. https://doi.org/10.1016/j.ejmech.2018.09.058.

5) Optimization of Existing Benzoxazole Scaffold. The study was initiated from a known E6446 hTLR9/hTLR7 antagonist. We provided a correlation between our binding mode hypothesis and hTLR9 antagonistic activity of series of molecules having characteristic molecular geometry, flexibility and basicity. The model could be used for future development (***European Journal of Medicinal Chemistry*, 2017**, 134, 334).



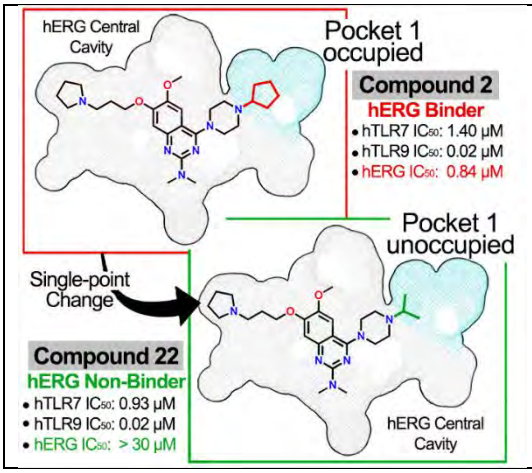
Design and Development of Benzoxazole Derivatives with Toll-like Receptor 9 Antagonism. Roy S, Mukherjee A, Paul B, Rahaman O, Roy S, Maithri G, Ramya B, Pal S, Ganguly D,* **Talukdar A***. ***European Journal of Medicinal Chemistry*, 2017**, 134, 334-347. https://doi.org/10.1016/j.ejmech.2017.03.086.

6) Design Facilitated by Universal Binding Model. The unusual topology of the ligand binding surface of TLR9 and TLR7 lacks conventional pockets. We proposed a hypothetical binding model to design TLR9 and TLR7 antagonists paving the way for a rational design (***European Journal of Medicinal Chemistry***, **2021**, 210, 112978; ***Molecules***, **2022**, 27, 13, 4026). Our hypothetical model was validated through the X-ray co-crystal structure of TLR7 published in Nature Comm. by Tojo et. al. doi: https://doi.org/10.1038/s41467-020-19025-z.



Synthesis and characterization of new potent TLR7 antagonists based on analysis of the binding mode using biomolecular simulations. Pal S, Paul B, Bandopadhyay P, Preethy N, Sarkar D, Rahaman O, Goon S, Roy S, Ganguly D,* **Talukdar A *.** ***European Journal of Medicinal Chemistry***, **2021**, 210, 112978.

7) Strategy to Mitigating hERG Liability. hERG is a primary **ANTI-TARGET in the drug development** process as the K+ channel encoded by hERG plays an important role in cardiac re-polarization. The present study describes a coordinated strategy to integrate the understanding from structure-based protein-ligand interaction to develop **non- hERG binders** with IC50 > 30 µM with retention of TLR7/9 antagonism through a ***single point change*** in the scaffold. This structure-guided strategy can serve as a prototype for abolishing hERG liability during lead optimization. (***ChemMedChem***, **2023**, e202300069. doi: 10.1002/cmdc.202300069).

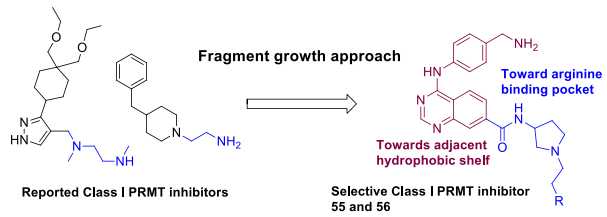


Mitigating hERG Liability of Toll-Like Receptor 9 and 7 Antagonists through Structure-Based Design. N Das, D Bhattacharya, P Bandopadhyay, UG Dastidar, B Paul, Rahaman O, Hoque I, Patra B, Ganguly D, **Talukdar A*.** ***ChemMedChem***, **2023**, e202300069. doi: 10.1002/cmdc.202300069).

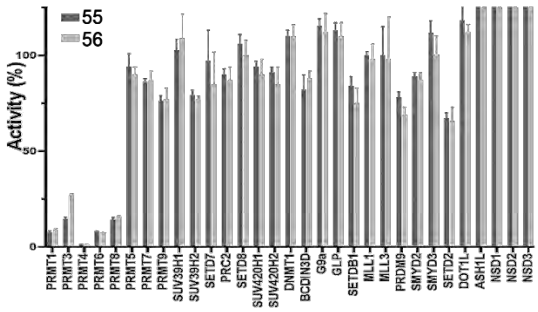
8) Fragment-Based Drug Design Strategy. We have developed selective class I protein arginine methyltransferase (PRMTs) inhibitors through a *fragment-based drug design approach*. PRMTs are enzymes that regulate epigenetic traits of multicellular organisms by catalyzing the methylation of

specific arginine residues which control chromatin compaction, cellular differentiation and repression or activation of transcription. However aberrant expression of methyltransferases is linked with diseases like cancer, diabetes, muscular disorders, neurodegenerative diseases, inflammatory disorders etc. Since epigenetic mutations are reversible in nature, a promising therapeutic approach includes targeting these aberrantly expressed epigenetic proteins. Several potent small molecule fragment inhibitors containing flexible alkyl amino side chains, thought to be a possible arginine mimic of Class I PRMTs are present in the literature, which are pan inhibitors of Class I PRMT.

Herein, we report the successful application of a fragment-based approach toward the discovery of selective Class I PRMT inhibitors. Structure-based ligand optimization was performed by strategic incorporation of fragment hits on the drug-like quinazoline core and subsequent fragment growth in the desired orientation towards the identified hydrophobic shelf. A clear SAR was established, and the lead compounds displayed potent inhibition of Class I PRMTs. We report the systematic development of potent Class I PRMT inhibitors with good potency and about 100-fold selectivity when tested against a panel of 31 human DNA, RNA, and protein lysine and arginine methyltransferases. The work was done in collaboration with the Structural Genomics Consortium (SGC Canada), where biological validations were done.



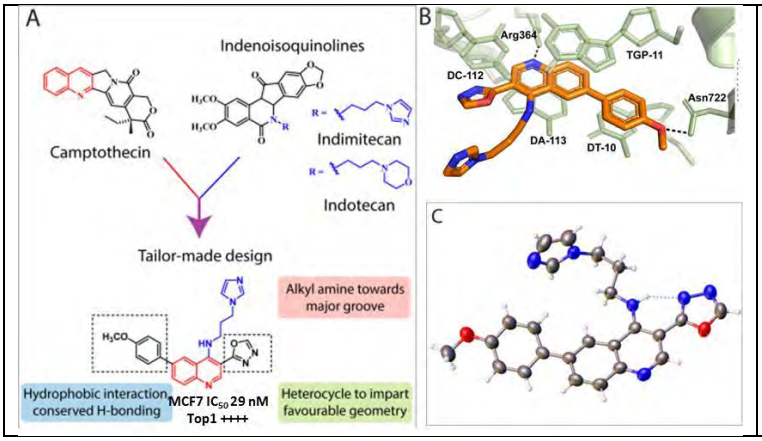
Fragment-based Design of Class I PRMT Inhibitor



Selectivity of lead candidates against a panel of 31 HMTs at 10 µM

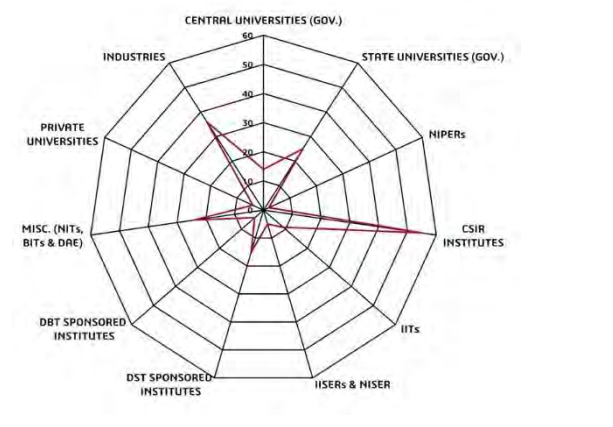
Development of Selective Class I Protein Arginine Methyltransferase Inhibitors through Fragment-Based Drug Design Approach. Bhattacharya D, Li ASM, Paul B, Dastidar UG, Santhakumar V, Sarkar D, Chau I, Li F, Ghosh T, Vedadi M, **Talukdar A.*** ***European Journal of Medicinal Chemistry*****, 2023,** *260*, 115713. https://doi.org/10.1016/j.ejmech.2023.115713

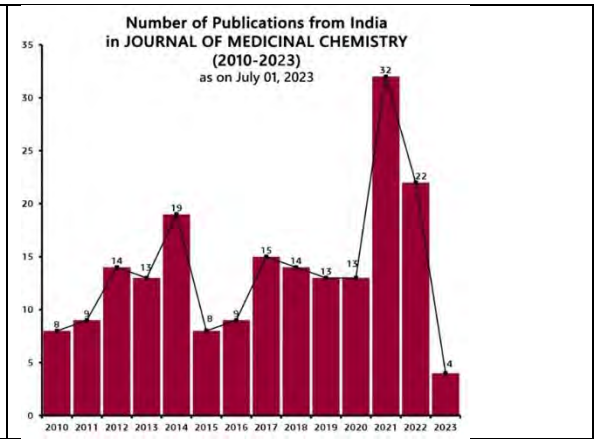
9) Hypothesis-driven tailor-made Topoisomerase 1 Poisons. *Here we have successfully developed and patented (WO2019229765) a new class of potent and selective Top1 poison based on the quinoline core with improved physicochemical properties as well as potency than camptothecin.* The design was initiated based on the structural features of known ligands/poison that bind through the network of interactions in the active site of the human Top1 enzyme. *Our selective lead Top1 poison is bicyclic in nature, unlike polycyclic camptothecins or indenoisoquinolines.* Strategically placed C4 nitrogen atom along with a heterocycle at the C-3 position would form an intramolecular hydrogen bonding (proved through crystal study), which imparts requisite polycyclic geometry and suitable curvature essential for stabilizing the Top1−DNA cleavage complex. Our Top1 poison does not intercalate with DNA nor react with Top1 enzyme but could stabilize covalent Top1-DNA intermediate to form a ternary complex. We have also provided mechanistic insight of Top1 inhibition through live cancer cell imaging and through mutation study. Unlike CPTs, they can stabilize Top1−DNA cleavage complexes even after 5 h proved by gamma-H2AX assay.



Discovery and Mechanistic Study of Tailor-Made Quinoline Derivatives as Topoisomerase 1 Poisons with Potent Anticancer Activity. Kundu B, Das SK, Paul Chowdhuri S, Pal S, Sarkar D, Ghosh A, Mukherjee A, Bhattacharya D, Das BB,* and **Talukdar A*.**
***Journal of Medicinal Chemistry*, 2019**, *62*, 3428.

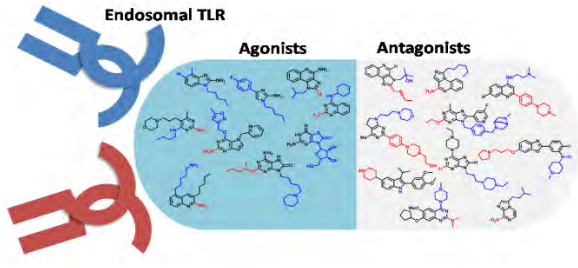
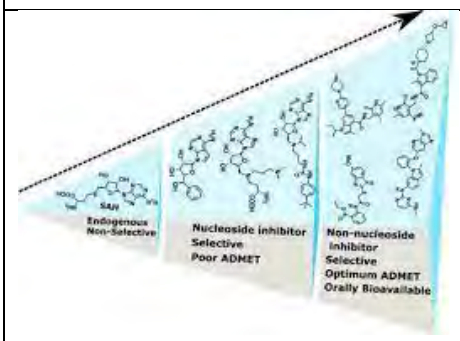
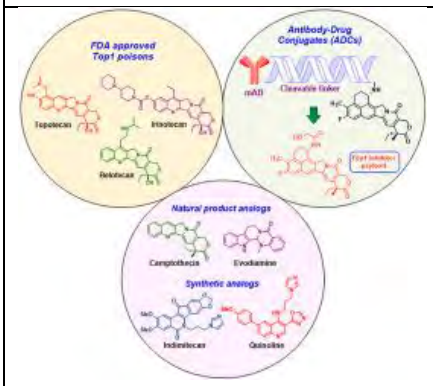
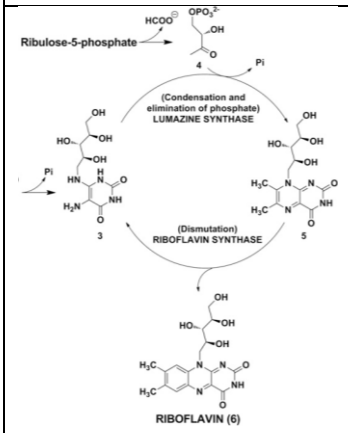
10) Editorial, Perspectives, and Review Articles for the Medicinal Research Community. Recently, I wrote an **Editorial in the Journal of Medicinal Chemistry** titled: Catalyzing the Future of Medicinal Chemistry Research in India. The Editorial provides a comprehensive look at more than a decade (2010 to midyear of 2023) of medicinal chemistry research in India, focusing on contributions to medicinal chemistry and drug discovery from both Indian academia and industries. The work provides an overview of cutting-edge medicinal chemistry research along with the organic-transformation-based chemical research scenarios in India in the past decade. It also distinguishes areas of research as well as contributions from different federal research institutes, state universities, central universities, and private universities by their geographical locations around India. The paper takes broader stock of the situation by comparing the articles published in the two internationally acclaimed journals in the field, viz. Journal of Medicinal Chemistry and Organic Letters, which highlights the current research trends as well as the thrust needed at the grass-roots level to boost medicinal chemistry and drug discovery research in India. *Finally, we believe that this discussion may create a pathway for policymakers and funding agencies to focus their efforts on motivating lesser inclined institutions as well as provide incentives to the institutions primarily involved in medicinal chemistry research, as they already have built capacity for such research.*





Talukdar A.*, Sarkar D. EDITORIAL: Catalyzing the Future of Medicinal Chemistry Research in India. ***Journal of Medicinal Chemistry*, 2023**, *66*, 10868. https://doi.org/10.1021/acs.jmedchem.3c01304

Perspective. Recently, we have published a couple of Perspectives and review articles in **J. Med. Chemistry, Eur J. of Med Chemistry and in Medicinal Research Reviews** providing comprehensive overview of the field by highlighting rational medicinal chemistry approaches for the benefit of the researchers in the field for the future development of potential lead candidates.

	Structural Evolution and Translational Potential for Agonists and Antagonists of Endosomal Toll-like Receptors. **Talukdar A**,* Ganguly D, Roy S, Das N, Sarkar D. ***Journal of Medicinal Chemistry***, **2021,** 64, 12, 8010.
	**Talukdar A.*** Mukherjee A, Bhattacharya D. Fascinating Transformation of SAM-Competitive Protein Methyltransferase Inhibitors from Nucleoside Analogues to Non-Nucleoside Analogues. ***Journal of Medicinal Chemistry***, **2022**, 65,3, 1662. **Selected for Special issue "Epigenetics 2022".**
	**Talukdar A.*** Kundu B, Sarkar D, Goon S, Mondal MA. Topoisomerase I inhibitors: Challenges, progress and the road ahead. ***European Journal of Medicinal Chemistry*, 2022**, 236, 114304.
	Kundu B, Sarkar D, Ray N, **Talukdar A.*** Understanding the Riboflavin Biosynthesis Pathway for the Development of Antimicrobial Agents. ***Medicinal Research Reviews***. **2019**, 1-34.

Regards

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