Ph. D. Open Seminar

Department of Chemistry, IISER Bhopal

Title of Thesis: N^2-modified Guanine Analogs - Synthesis and Biological Applications

Speaker: **Bapurao Arjun Bhoge** Roll No.: 1320202

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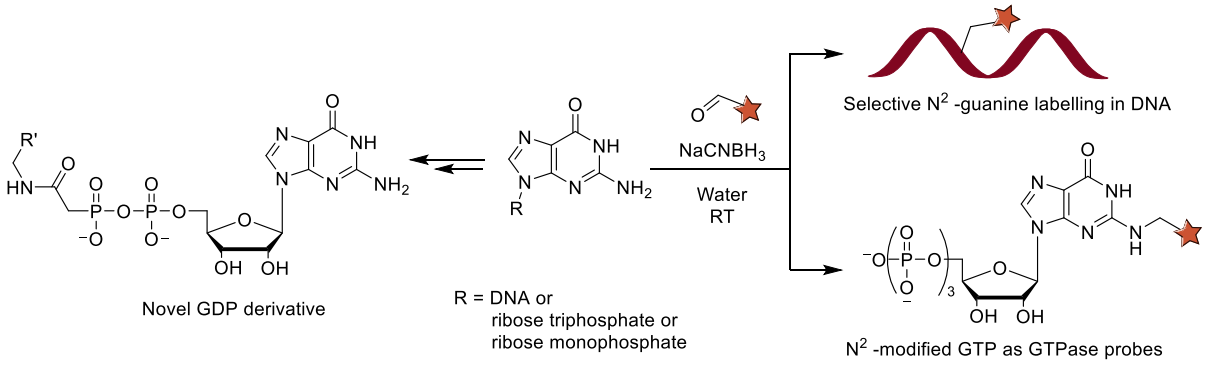
Guanine nucleotides are versatile not only as substrates for DNA and RNA biosynthesis, but also as important regulators of various signaling pathways. Their ability to form G-quadruplex structures have also been used in nanotechnology to obtain well-defined architectures, as well as in medicinal chemistry as antiviral agents.[1] Guanine nucleotide analogs have been used as probes to study and manipulate biological functions. For example, N^2-adducts at guanine nucleobase in DNA are mutagenic and are often used to study the effect of these lesions on DNA replication.[2] Despite their immense importance, available methods to access these oligonucleotides and nucleotide triphosphates are challenging, time-consuming, and expensive; and necessitate the development of new synthetic methods.

We have employed reductive amination to selectively functionalize the N^2-amine of guanosine. We find that this simple yet powerful reaction could selectively modify the N^2-position of guanosine, leaving the other aromatic exocyclic amine bases (viz. cytosine and adenine) unaffected under the reaction conditions. Aliphatic aldehydes of intermediate hydrophobicity (logP < 1.2) could efficiently react in aqueous medium, modifying the N^2-position of guanine both in nucleotides and in nucleic acid polymers.[3] We demonstrated the utility of this method for site-specific fluorescent labeling of DNA oligonucleotides by employing the reactivity of a bio-orthogonal handle installed onto the N^2-position of guanine using our reductive amination strategy. Further, N^2-substituted guanosine triphosphates made via this route were substrates for GTPase proteins establishing them as GTP mimics. In another study, we designed and synthesized novel β-phosphate substituted guanosine nucleotide analogs as potential GTP and GDP mimics. In summary, our work provides easy access to guanine analogs for potential biological applications.



[1] L. Stefan, D. Monchaud, *Nat. Rev. Chem.,* 2019, **3**, 650-668

[2] (a) C. Ebert, N. Simon, S. Schneider,and Thomas Carell, *ChemBioChem*, 2017, **18**, 1379 – 1382; (b) A. S. P. Gowda, M. Lee, and T. E. Spratt, *Angew. Chem. Int. Ed.* 2017, **56**, 2628 –2631, (C) C. J. Lech and A. T. Phan, *Nucleic Acids Res.*, 2017, **45**, 6265–6274, (d) S. Seidu-Larry, B. Krieg, M. Hirsch, M. Helm and Domingo *Chem. Commun.,* 2012, **48**, 11014–11016

[3] B. A. Bhoge and I. Saraogi, *(Manuscript under Preparation)*