

Thesis title: *Insights into Nucleic Acid Secondary Structures and Biomimetic Synthetic Ion Channels by Molecular Probes*

Abstract

Nucleic acid secondary structures have evolved as important therapeutic targets in cancer and infectious diseases. The G-rich sequences of human genome hold the potential to form DNA or RNA secondary structures known as G-quadruplexes (G4s). Stabilization of G4 structures by small molecules could lead to the development of anticancer as well as antiviral therapeutics and diagnostics. The proto-oncogenes like *c-MYC*, *c-KIT*, *BCL-2* promoters and human telomeres contain guanine-loaded sequences to form G4 structures. *c-KIT* and *c-MYC* proto-oncogenes play critical role in cell proliferation and differentiation, cellular growth and apoptosis. Mutation in *c-KIT* or *c-MYC* proto-oncogene could lead to the development of leukemia and breast cancer like critical diseases. The thesis consists of introduction, three chapters, conclusion and an experimental section. The first chapter describes targeting oncogenic G4s by molecular probes, and is subdivided into two sections. In the first section (Chapter 1A), a thiazole based G4 sensing polyamide has been developed, which recognizes G4 structures and represses *c-KIT* proto-oncogene expression in leukemia cells. Owing to excellent fluorescence enhancement property inside the cells, the polyamide has been used as molecular probe to image the cellular system. In the next section (Chapter 1B), a series of thiazole based peptide ligands have been studied, which show highest stabilization potential as well as high binding affinity for the *c-MYC* G4. One of the ligands represses *c-MYC* oncogene expression in breast cancer cells. The peptidomimetic ligand exhibits potent toxicity towards the cancer cells while it does not show toxicity for the normal cells. The nuclear localization and intracellular fluorescence property make it a unique molecular scaffold to probe biological system.

The ongoing SARS-CoV-2 (COVID-19) pandemic has inspired us to work on small molecule based antiviral therapeutics due to its deadly combination of high infection and mutation rate. In Chapter 2, the G-rich sequences present in CoV-2 genome have been first characterized to identify the putative G-quadruplex structures. The RNA G-quadruplex structures *RG-1*, *RG-2* and *RG-3* present in the CoV-2 genome could be a potent therapeutic target for the development of small molecule drugs. A coumarin based peptidomimetic has been developed that preferentially binds to the *RG-2* motif of SARS-CoV-2 over duplex DNA. This

peptidomimetic ligand may lead to further development of small molecule based therapeutics for COVID-19.

The Chapter 3 describes the development of bioinspired ion channels from synthetic molecules. This chapter is divided into two subsections. The first section (Chapter 3A) describes ion channel formation using a G-quadruplex binding peptidomimetic ligand. The fabrication of artificial ionophores with G4 selective chemotherapeutic small molecules has not been explored so far. An artificial ion channel has been constructed with a G4 specific thiazole based peptidomimetic that forms nanovesicular and nanofibrillar structures allowing transportation of Na^+ and K^+ via model lipid bilayer membrane with high ionic conductance. Besides, the peptidomimetic ligand preferentially binds to *c-MYC22* G4 with high affinity and inhibits *c-MYC* oncogene expression at m-RNA level following cancer cell death. This study would provide critical structural and functional aspects of artificial ion channels and open up a new paradigm for developing novel synthetic ion transporters with improved therapeutic potential.

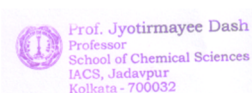
Inspired from naturally occurring guanosine, the next study describes the formation of highly conductive transmembrane nanopore from folate guanosine derivatives (Chapter 3B). The folate guanosine derivatives span the lipid membrane and transport Na^+ and K^+ with very high conductance indicating the formation of large pore via cell membrane mimicking artificial lipid bilayer. In addition, the ligands allow the influx of small molecular cationic dye through GUV membrane, which again demonstrates the folate mediated construction of stable nanoporous structure. This work would shed light on designing membrane nanopores by naturally derived or bioinspired molecules as ion transporters that would find applications in drug delivery systems, and biosensing.

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