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Discovery of small molecule DNA G-Quadruplex stabilizing agents: Design, synthesis and biological studies

Mrinalkanti Kundu
TCG Lifesciences Pvt. Ltd., India

DNA has played a key role as a molecular target for many of the drugs that have been used for decades in cancer therapeutics. Compounds that target DNA are some of the most effective agents in clinical use and produced increase in cancer patients' survival but, they are extremely toxic. Consequently, enormous effort has been put into finding more selective agents; thus, there is considerable excitement in identifying cancer-specific DNA targets and thereby resulting in less toxic new therapeutics. This has driven interest in targeting unusual, non-canonical structures of DNA, in order to achieve selectivity while potentially reducing adverse side effects. Accordingly, cell-permeable specific probes targeting G-quadruplex structures should provide researchers with new tools for studying their potential involvement in gene expression, chromosome stability, viral integration and recombination. Significant research is in progress targeting G-quadruplex DNA with small molecules hoping to inhibit cancer growth according to two distinct mechanisms; first, promoter deactivation and second, inhibition of telomerase which is responsible for maintaining length of telomeres, and is involved in around 85% of all cancers. We wish to report the design, synthesis of novel drug-like small molecules and their biological evaluation as potential G-quadruplex stabilizing agents. Efficiency of these synthetic compounds for the stabilization of promoter quadruplex DNA structures was performed along with thorough investigation to assess the quadruplex binding affinity by using various biophysical and biochemical studies. For some of the compounds, the binding mode was explained by molecular modelling studies and their potential anti-cancer inhibitory effect was also tested.

Biography

Mrinalkanti Kundu is a Medicinal Chemist and carries 13 years of experience in small molecule therapeutics via orthosteric/allosteric modulation of GPCR, ion channels and enzymes with a track record in delivering pre-clinical candidates for metabolic disorders, pain, oncology and anti-infective programs. He completed his MSc and PhD from Indian Institute of Technology in Bioorganic Chemistry and was awarded Post-doctoral Fellowships in the field of Chemical Biology from University of Uppsala, National Institute on Aging, in collaboration with The Johns Hopkins University and University of Basel and published 10 patents, 15 articles and 1 book chapter.

mrinal.kundu@tcgls.com

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