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Biophysical Study of the Interaction of Harmalol with Nucleic Acids of Different Motifs: Spectroscopic and Calorimetric Approaches

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Abstract : Binding of small molecules to DNA and recently to RNA, continues to attract considerable attention for developing effective therapeutic agents for control of gene expression. This work focuses towards understanding interaction of harmalol, a dihydro beta-carboline alkaloid, with different nucleic acid motifs viz. double stranded CT DNA, single stranded A-form poly(A), double-stranded A-form of poly(C)·poly(G) and clover leaf tRNAphe by different spectroscopic, calorimetric and molecular modeling techniques. Results of this study converge to suggest that (i) binding constant varied in the order of CT DNA > poly(C)·poly(G) > tRNAphe > poly(A), (ii) non-cooperative binding of harmalol to poly(C)·poly(G) and poly(A) and cooperative binding with CT DNA and tRNAphe, (iii) significant structural changes of CT DNA, poly(C)·poly(G) and tRNAphe with concomitant induction of optical activity in the bound achiral alkaloid molecules, while with poly(A) no intrinsic CD perturbation was observed, (iv) the binding was predominantly exothermic, enthalpy driven, entropy favoured with CT DNA and poly(C)·poly(G) while it was entropy driven with tRNAphe and poly(A), (v) a hydrophobic contribution and comparatively large role of non-polyelectrolytic forces to Gibbs energy changes with CT DNA, poly(C)·poly(G) and tRNAphe, and (vi) intercalated state of harmalol with CT DNA and poly(C)·poly(G) structure as revealed from molecular docking and supported by the viscometric data. Furthermore, with competition dialysis assay it was shown that harmalol prefers hetero GC sequences. All these findings unequivocally pointed out that harmalol prefers binding with ds CT DNA followed by ds poly(C)·poly(G), clover leaf tRNAphe and least with ss poly(A). The results highlight the importance of structural elements in these natural beta-carboline alkaloids in stabilizing different DNA and RNA of various motifs for developing nucleic acid based better therapeutic agents.

Keywords : calorimetry, docking, DNA/RNA-alkaloid interaction, harmalol, spectroscopy
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