Assessment of Molecular Binding of Hoechst 33258 Analogues into DNA using Docking and MM/GBSA Approach

U. Issar, T. Kumari and R. Kakkar*

Computational Chemistry Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India

*Author for correspondence e-mail: rkakkar@chemistry.du.ac.in

In order to understand every aspect of interaction between minor groove binders based on Hoechst 33258 and the double helical B-DNA dodecamer, a molecular modeling study has been performed on Hoechst analogue-DNA complexes. Using combinatorial design with structural modifications, a diverse ligand library of two hundred and fifty analogues of Hoechst 33258 has been prepared. Molecular interactions and binding affinities of these analogues, differing in their central cores, with nucleic acids are studied using molecular docking and MM-GB/SA methods. Results show that the presence of hydrogen bond donors, aliphatic piperazinyl ring and rotatable bonds is the essential requirement for optimal DNA binding of Hoechst analogues. Mainly, the bi-substituted and tri-substituted phenyl analogues, rich in hydrogen bond donors, display good recognition towards AATT rich DNA sequences, affirming all reported experimental observations. The analogues that have benzoxazole, benzothiazole and pyridine substituted benzimidazole show preference towards GGCC rich DNA rather than CCGG, AATT and TTAA rich DNA. From the induced fit docking analysis, we have found that the binding site of these analogues consists mainly of GCCA or TGGC sequences. Here, the guanine base acts as both a hydrogen bond donor and hydrogen bond acceptor for these heteroatom substituted analogues, thereby holding them with greater ease. In all, our work satisfactorily explains the variation in drug-DNA recognition on altering the basic nature of Hoechst.