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Binding behaviour of aminoglycoside drug kanamycin with calf thymus DNA: Thermodynamic, spectroscopic and molecular modelling studies

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ABSTRACT

In this work, the binding mode of antibiotic drug kanamycin with Calf thymus DNA (ctDNA) was assessed using thermodynamic, spectroscopic and molecular docking studies. Isothermal Titration Calorimetry (ITC) studies suggest that the binding is enthalpically favored with a small entropic change and a binding constant of the order of 10^4 mol $^{-1}$ dm^3, which remains almost same in the studied temperature range. Studies in the presence of osmolytes tetraethylene glycol and sucrose show no appreciable change in the binding behaviour as well as on the stability of the DNA-kanamycin complex. These finding suggests that the number of water molecule released or taken up is not significant in the binding process. Competitive fluorescence displacement assay and circular dichroism studies show that kanamycin follows groove binding mode of interaction. Molecular docking studies also supports that kanamycin prefers groove binding mode, stabilized by hydrogen bonding.

1. Introduction

DNA serves as a carrier of genetic information of cells and involved in indispensable life processes such as DNA replication, transcription, and protein synthesis. DNA is an intracellular target for many anticancer drugs, which alter its vital functions in proliferating cells such as cancer cells [1]. These small molecules modify, activate, or inhibit DNA functions and therefore can be used as therapeutics for the treatment of diseases. The study of DNA drug interaction helps to gain more insight into the mode of action of these drugs at the molecular level. These studies also help in the optimization of the clinical efficacy of existing drugs to find out their toxicological and pharmacological behavior of the drug. Moreover, some drugs have hidden targets that are yet unknown. Depending upon the biological activity of the drugs, these properties may lead to toxicity or can be used as alternative therapeutics of these drugs [2]. One of the most challenging goal is to design molecules which specifically target disease related sequences with high selectivity. Triple helix formation is one of the strategies in that direction [3,4].

Aminoglycoside drugs are not specific to RNA only but this drug family targets nucleic acids that can adopt the A-conformation like DNA-RNA hybrid duplex [5], RNA duplex [6], DNA triplex and RNA triplex [7], A-form DNA duplex [8]. These kind of structure- activity relationship behaviour can only be understood by determining different forces which are responsible for binding of biomolecules with small molecules. Binding forces or behaviour are well understood by employing different biophysical studies [9–15]. Therefore, these studies can be further directed to synthesize target-oriented drugs.

Kanamycin is a water-soluble aminoglycoside antibiotic produced by fermentation of *Streptomyces kanamyceticus* [16], and its chemical structure is shown in Fig. 1. It was reported to interact with the small subunit of ribosomes and cause codon misreading [16–18].

Aminoglycosides are known to induce codon misreading in translation process [17]. The hydroxyl groups of aminoglycosides act as metal donors. Metalloaminoglycosides such as Cu^{2+}- kanamycin and Cu^{2+}- neamine have shown far better cleavage activity of DNA than that of enzymes [19,20]. The interaction of kanamycin with the duplex DNA has not been reported in the literature, though its effect on the stability of triplex helix has been reported by Coffee and Arya [21].

In order to understand the binding of kanamycin with the triple helical DNA, it is essential to study its interaction with duplex DNA. Such studies on duplex DNA are required to identify the type of structural requirement of DNA. Therefore, in the present work we have aimed at understanding the interaction of Kanamycin with calf thymus DNA by using a combination of calorimetric and spectroscopic techniques to address the energetic and conformational aspects.

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