SPECTROSCOPIC AND MOLECULAR DOCKING EVIDENCE OF DICLOFENAC AND MEFENAMIC ACID BINDING TO DNA

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Non-steroidal anti-inflammatory drugs (NSAIDs) are used in treatments such as inflammatory, analgesics and anti-pyretic by interacting with cyclooxygenase and forming prostaglandins. The study of the interaction of NSAIDs with DNA is very sensitive and significant not only in understanding the mechanism of the interaction but also in new drug designing. Diclofenac and mefenamic acid are different classes of drugs called non- steroidal anti-inflammatory drugs. A set of biophysical experiments such as UV-visible spectroscopy, Fluorescence spectroscopy and viscosity measurement studies and molecular docking studies were conducted to investigate the interaction mechanism of DNA with small molecules. The software- aided molecular docking plays an important role in the drug design as well as in the mechanistic study by placing the molecule into the binding site of a target macromolecule in a non-covalent fashion.

The binding constant of diclofenac and mefenamic Acid from UV – visible experiment was found to be 2.05×10^4 M^{-1} and 2.73×10^4 M^{-1}, respectively. The corresponding value of fluorescence experiments of diclofenac and mefenamic acid was 8×10^{-3} µl ng^{-1} and 6×10^{-3} µl ng^{-1}. Both, binding constant and fluorescence experimental values showed that the diclofenac indicates a relatively higher affinity to DNA due to two chloride substitutions, which promote inter-molecular hydrogen bonding with DNA backbone. Apart from that, hyperchromism and hypochromism are the two main effects that can be observed with the increasing concentration of DNA and measuring the effect at a particular wavelength. The drugs diclofenac and mefenamic acid are resulting in the tendency of hypochromism. This is because when the drug molecule binds to the DNA, the orbital of the binding ligand could couple with an orbital of base pairs in the DNA. The coupling orbital will be partially filled by electrons, thus leading to a decrease in the transition probabilities.

The classical intercalators often result in increased viscosity of DNA solution due to the lengthening of DNA duplex as base pairs are unwound to accommodate such ligands. Yet, in the case of groove binders, if there is no noticeable increase in the viscosity of DNA solution, relatively small changes in viscosity can be considered for groove binders. The molecular docking studies exposed both drugs showing binding with DNA in minor grooves. The resulting relative binding energy of respective docked complexes (diclofenac and mefenamic acid) was found to be -6.0 kcal/ mol and -5.8 kcal /mol respectively. They resulted in

the minor groove binding mode because of the narrow pocket area. Small molecules interact with minor groove when large molecules tend to be bound at the major groove. It was confirmed that the molecular docking results are in approximate correlation with the studied experimental results.

Keywords: Molecular docking, NSAIDs, DNA

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