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Evaluation of calf thymus DNA binding of newly synthesize five 9 —O— Imidazolyl alkyl berberine derivative: A comparative multi-spectroscopic and calorimetric study

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ABSTRACT

DNA binding with small molecule plays an important role in the designing of various anticancer drugs with greater efficacy. The five 9-O-imidazolyl alkyl berberine derivatives (BI) of different chain length has been synthesized and fully characterized. The binding study of calf thymus DNA with these newly synthesized berberine derivative was performed using various biophysical techniques. The binding affinity of BI to calf thymus DNA increased with increasing the chain length. The binding constant value obtained from UV–Vis spectral analysis was $1.84x10^5$for BI1, $2.01x10^5$for BI2, 1.51×10^6 for BI3, 3.66×10^6 for BI4, 6.68×10^6. Partial intercalative binding with strong stabilization of the DNA helix was revealed from circular dichroism spectral study and viscosity measurement. From the ITC experiment it was revealed that the bindings of BI1, BI2, BI3, BI4 and BI5 to calf thymus DNA were favoured by a large positive favourable entropy and negative enthalpy change and the highest spontaneity found for BI5. With the increase in chain length the binding was driven by a stronger entropy term with a higher binding constant indicates involvement of hydrophobic force for all these interaction. High binding affinities of calf thymus DNA with berberine-imidazole derivatives might be helpful for new drug design.

1. Introduction

Berberine, a protoberberine isoquinoline group of quaternary ammonium alkaloid, is mostly found in plants such as Berberis, Berberisaristata, Coptischinensis, Tinosporacordifolia and to a smaller extent in Argemonemexicana. Its anti-inflammatory and antibacterial properties are well known from the ancient time and used as traditional medicine in many country [1–3]. It also has been utilized for thousands of years to treat parasitic intestinal infection and diarrhea [4]. Many pharmacological studies of berberine have performed to reveal its biological activities, such as anti-oxidant [5,6], anti-inflammatory [7–9], anti-bacterial [10–12], anti-diabetic [13–15], anti-tumor [16–18], viricide [19–21], cardiovascular protection [22–24], antineuro degeneration [25–27], hypolipidemic [28,29], anti-ulcer [30,31] and anti-rheumatoid arthritis [32,33]. In recent years, many study revealed that berberine can constrain the growth of cancer cell through diverse mechanisms such as cell cycle regulation, autophagy, inducing apoptosis, repressing cell invasion and metastasis, regulating tumor micro-environment, by immunomodulation, interacting with micro ribonucleic acids (microRNAs) and suppressing telomerase activity, etc. [17,18,34–36]. Furthermore, it was reported that berberine possesses significant cytotoxicity against human cancer cell lines and the reason lies in the fact that berberine is a good DNA-binder. Therefore researcher has been widely studied its DNA binding property [37,38].

According to current literature survey, Wan-Jin Zhang et al. synthesized 9-substituted berberine derivatives, 9-O-(*N,N*-dimethyl propoxy) berberrubine chloride, 9-O-(N,N-diethyl propoxy)berberrubine chloride, 9-O-piperazinylpropoxy berberrubine chloride,9-O-pipyridinepropoxy berberrubine chloride and their binding constant are $3.06x10^6M^{-1}$,$3.03 \times 10^6\ M^{-1}$, $3.01 \times 10^6\ M^{-1}$ and $3.52x10^6M^{-1}$ respectively [39].

Khatun et al. also showed that with increasing the cycloalkane ring size of the substitution at 9-O-position, the binding affinity also increases and in all cases the binding affinity is higher than the mother

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