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Interaction of anthraquinone anti-cancer drugs with DNA:Experimental and computational quantum chemical study

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ABSTRACT

Anthraquinones form the basis of several anticancer drugs. Anthraquinones anticancer drugs carry out their cytotoxic activities through their interaction with DNA, and inhibition of topoisomerase II activity. Anthraquinones (AQ4 and AQ4H) were synthesized and studied along with 1,4-DAAQ by computational and experimental tools. The purpose of this study is to shade more light on mechanism of interaction between anthraquinone DNA affinic agents and different types of DNA. This study will lead to gain of information useful for drug design and development. Molecular structures were optimized using DFT B3LYP/6-31 + G(d). Depending on intramolecular hydrogen bonding interactions two conformers of AQ4 were detected and computed as 25.667 kcal/mol apart. Molecular reactivity of the anthraquinone compounds was explored using global and condensed descriptors (electrophilicity and Fukui functions). Molecular docking studies for the inhibition of CDK2 and DNA binding were carried out to explore the anti cancer potency of these drugs. NMR and UV-VIS electronic absorption spectra of anthraquinones/DNA were investigated at the physiological pH. The interaction of the three anthraquinones (AQ4, AQ4H and 1,4-DAAQ) were studied with three DNA (calf thymus DNA, (Poly[dA].Poly[dT]) and (Poly[dG].Poly[dC]). NMR study shows a qualitative pattern of drug/DNA interaction in terms of band shift and broadening. UV-VIS electronic absorption spectra were employed to measure the affinity constants of drug/DNA binding using Scatchard analysis.

1. Introduction

The development of novel potent chemotherapeutics has been a topic of interest for decades [1–4]. DNA is a primary target for drugs in the cell. The mode of action of many chemotherapeutic agents is thought to be due to their ability to intercalate between double helix DNA base pairs. Originally, this model was first suggested in 1961 by Lerman in the context of the acridines and DNA interaction. These chemotherapeutics are generally thought to exert their biological actions through binding with DNA followed by an interference with DNA replication, transcription, and inhibition of gene expression. The design of small drug molecules that selectively target DNA, with high binding affinities, has led to the discovery of many anticancer, antibiotic, and antiviral drugs [5–14].

Quinonoid compounds are a series of widespread compounds found in the living organisms. These compounds are known to perform many biochemical and physiological processes in living organisms. Quinones are organic compounds with various interesting antitumor, antibacterial, antibiotical, and antifungal properties [15,16]. Anthraquinones, as a group of natural quinones, are widely used in treatment of cancer. Anthraquinones anticancer drugs carry out their cytotoxic activities through their interaction with DNA, preferentially at guanine/cytocine rich sites. This interaction is believed to cause significant conformational changes in the DNA leading to inhibition of the DNA replication [17]. This may lead to DNA damage. On the other hand, they can cause inhibition of topoisomerase II activity, leading to DNA damage.

Most DNA-targeted molecules start their binding with double helix DNA non-covalently which subsequently may developed to covalent binding. Non-covalent binding may include π-stacking,

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hydrogen bonding, electrostatic, charge transfer, and hydrophobic interactions [17]. All these interactions may contribute to the drug/DNA interaction mechanism so that the main objective of this study is to explore the dominant interaction. This information is crucial for design and development of new drugs. Molecular docking of anthraquinones with DNA and Cyclin-dependent kinase-2 (CDK2) will shed more light on the binding modes of these drugs with biological molecules. CDK2 takes an important part in regulating various events of living cell cycle. Therefore, CDK2 is considered as a potentially therapeutic target for cancer therapy. In addition to DNA CDK2 was chosen for our study as some anthraquinone derivatives showed a good inhibitory effect toward CDK2 enzyme. For this study the following anthraquinone derivatives (Scheme 1), 1,4-bis {[2-(methylamino)ethyl]amino}-5,8-dihydroxyanthracene-9,10-dione, (AQ4), 1,4-bis {[2-(methylamino)ethyl]amino}anthracene-9,10-dione, (AQ4H) and 1,4-diaminoanthraquinone were chosen for this study.

2. Experimental details

The UV-VIS absorption spectra were measured using a Perkin Elmer Lambda-16 UV-VIS Spectrophotometer. NMR spectra were recorded in $CDCl_3$ using a Bruker AC250 at 30 °C.

Calf thymus DNA, polydeoxyadenylic acid-polythymidylic acid (Poly[dA]. Poly[dT]) and polydeoxyguanylic acid-polydeoxycytidylic acid (Poly[dG]. Poly[dC]) were purchased from Sigma Chemical Co and were used without further purification. 1,4-DAAQ and D_2O (99.9% D) were purchased from Aldrich. Trizma base (Tris[hydroxymethyl] aminomethane) and NaCl were supplied from Sigma and used for buffer preparation without further purification.

2.1. Synthesis of anthraquinone drugs

1,4-bis {[2-(methylamino)ethyl]amino}-5,8-dihydroxyanthracene-9,10-dione, (AQ4), 1,4-bis {[2-(methylamino)ethyl]amino}anthracene-9,10-dione, (AQ4H) were synthesized according to the following method [18–20]:

2.1.1. AQ4 synthesis

The synthesis of AQ4 was done in three steps;

1 *Synthesis of 1,5-diamino-4,8-dihydroxy anthracene-9,10-dione.* A stirred solution of 1,5-DAAQ (6 g, 25 mmol) in concentrated sulphuric acid (97%) was maintained at −5 °C. Anhydrous sodium chlorate (7.2 g, 67 mmol) was slowly added over 30 min. The mixture was allowed to warm to room temperature and stirred for further 3 h. A precipitate resulted on slowly adding a chilled solution of 1000 cm^3 of 1% sodium hydrogen sulfite, which, was removed by filtration and washed thoroughly with water and freeze-dried to yield (6 g, 88%) of title compound.

2 *Synthesis of leuco-1,4,5,8-tetrahydroxyanthracene-9,10-dione.* A stirred mixture of 1,5-diamino-4,8-dihydroxyanthracene-9,10-dione (5 g, 19 mmol) and sodium hydroxide (10 g, 25 mmol) in water was heated under reflux for 3 h until ammonia was no longer evolved and the solution colour turned blue to brown. The solution was allowed to cool to room temperature and then acidified to pH 3 with 5 M HCl. The resulting precipitate was removed by filtration and washed with water and dried to afford (4.5 g, 75%) of brown powder.

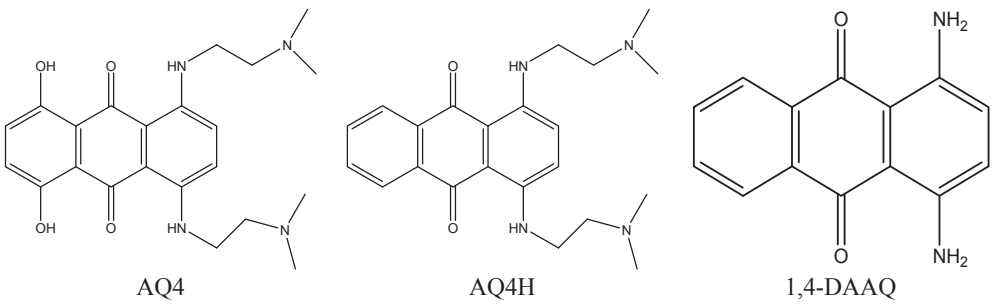
3 *Synthesis of 1,4-bis{[2-(methylamino)ethyl]amino}-5,8-dihydroxyanthracene-9, 10-dione.* A partial solution of leuco-1,4,5,8-tetrahydroxyanthracene-9,10-dione (1 g, 3.6 mmol) and 10 ml of N,N-dimethylethylendiamine in 50 ml of ethanol was heated under reflux for 1 h under an atmosphere of argon and then allowed to cool at room temperature. The suspension was stirred at room temperature for 24 h to open air. Aqueous sodium hydroxide solution (5 M, 0.5 cm^3) was added and stirred for 1 h. The solvent was removed under vacuum and gave the resulting dark blue powder (0.6 g, 40%) after recrystallization from ethanol as the titled compound. R_f (9:1:0.1 CH_2Cl_2/MeOH/H_3N):0.33. ^1H NMR δ ($CDCl_3$): 7.15 (s, 2H), 7.10 (s, 2H), 3.45 (m, 4H), 2.65 (t, 4H), 2.35 (s, 12H); ^{13}C NMR δ ($CDCl_3$): 185, 156, 147, 125, 126, 116, 109, 58, 46, 41; mass spectrum, m/z 413 ($m^+ + 1$). IR ν (KBr): 3500, 3100, 2800, 1650, 1625, 1475, 1375, 1465, 1225, 850 cm^{-1}. Anal. Calcd. For $C_{22}H_{28}O_4N_4.025H_2O$: C, 63.3; H, 7.0; N, 13.4. Found: C, 63.3; H, 7.0; N, 13.4.

2.1.2. AQ4H synthesis

A partial solution of leucoquinizarine (2 g, 8.3 mmol) and N,N-dimethylethylendiamine (10 ml) was heated under reflux for 8 h under an atmosphere of argon and then allowed to cool at room temperature. The suspension was stirred at room temperature for 24 h to open air and diluted with water to precipitate the title compound. The filtered solid was washed with water and dried. The solid was chromatographed (SiO_2, (9:1 CH_2Cl_2/MeOH; 9:1:21 CH_2Cl_2/MeOH/NH_3), then washed with hexane and recrystallized from ethanol giving the title compound. ^1H NMR δ (CD_3OD): 8.3 (q,2H), 7.75 (q, 2H), 7.38 (s, 2H), 3.45 (m, 4H), 2.7 (t, 4H), 2.4 (s, 12H); ^{13}C NMR δ ($CDCl_3$): 187, 158, 149, 138, 135, 129, 128, 62, 48, 44; mass spectrum, m/z 381 ($m^+ + 1$). Anal. Calcd. For $C_{22}H_{28}O_2N_4$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.50; H, 7.22; N, 14.81.

3. Computations

All computations were done using G09 suit of programs [21]. Molecular geometry of anthraquinone compounds were optimized in the gas phase at DFT B3LYP/6-31 + G(d,p) level of theory. A



Scheme 1. Studied anthraquinones.