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Synthesis of novel anthraquinones: Molecular structure, molecular chemical reactivity descriptors and interactions with DNA as antibiotic and anti-cancer drugs

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ABSTRACT

Anthraquinones are well-known anticancer drugs. Anthraquinones anticancer drugs carry out their cytotoxic activities through their interaction with DNA, and inhibition of topoisomerase II activity. Anthraquinones (AQ5 and AQ5H) were synthesized and studied with 1,5-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 four conformers of AQ5 were detected within the range of about 42 kcal/mol. Molecular reactivity of the anthraquinone compounds was explored using global and condensed descriptors (electrophilicity and Fukui functions). NMR and UV–VIS electronic absorption spectra of anthraquinones/DNA were investigated at the physiological pH. The interaction of the anthraquinones (AQ5 and AQ5H) were studied with different DNA namely, calf thymus DNA, (Poly[dA].Poly[dT]) and (Poly[dG].Poly[dC]). UV–VIS electronic absorption spectral data were employed to measure the affinity constants of drug/DNA binding using Scatchard analysis. NMR study confirms qualitatively the drug/DNA interaction in terms of peak shift and broadening.

1. Introduction

Quinone-containing compounds are a series of widespread compounds found in nature. Quinones and quinone-derivatives are important class of molecules, having high importance in dye industry, biology and pharmaceutical chemistry [1–7].These compounds are known to perform many biochemical and physiological processes in living organisms. Anthraquinones, as a group of natural quinones, are widely used in treatment of cancer [8–11]. Anthraquinones anticancer drugs carry out their cytotoxic activities through their interaction with DNA, preferentially at guanine/cytocine rich sites [12]. This interaction is believed to cause significant conformational changes in the DNA leading to inhibition of the DNA replication [12]. This may lead to DNA damage. On the other hand, they can cause inhibition of topoisomerase II activity, leading to DNA damage. The development of novel potent chemotherapeutics and design of small drug molecules that selectively target DNA, with high binding constants, has led to the discovery of many anticancer, antibiotic, and antiviral drugs [13–21]. 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, hydrogen bonding, electrostatic, charge transfer, and hydrophobic interactions [12]. 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 anthraquinone antibiotic and anticancer drugs.

Of the anthraquinones, the ones having hydroxy and amino substituents have been extensively investigated, to understand their biochemical activity [22–34]. For this study the following amino and hydroxy anthraquinone derivatives (Scheme 1), 1,5-bis {[2-(methylamino)ethyl]amino}-4,8-dihydroxy anthracene-9,10-

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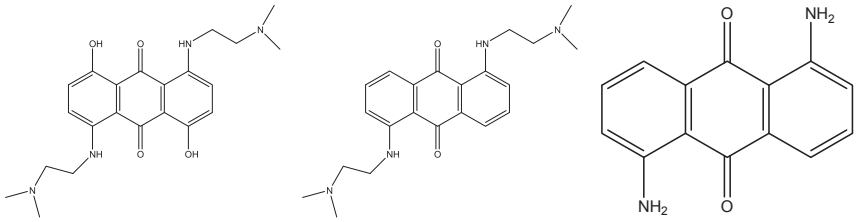

Scheme 1. Studied anthraquinones.

dione, (AQ5), and 1,5-bis{[2-(methylamino)ethyl]amino}anthracene-9,10-dione, (AQ5H) and 1,5-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 utilizing these experimental parameters: 250 MHz, 5.9 T, 5 mm multinuclear broadband probe, Receiver Gain RG = 8, Pulse Width PW = 4, Relaxation Delay RD = 2 and Number of Scan NS = 8. DNA concentrations per nucleotide were determined spectrophotometrically using the molar absorption coefficient: $\varepsilon_{260} = 6600\ M^{-1}\ cm^{-1}$ to be 1.061×10^{-4} M. NMR spectra of drug/DNA mixtures were measured at 30 °C. Two or three mixture solutions were produced by accurate dilution from the stock solutions keeping AQs concentration constant while varying the concentration of the DNA, were run and compared with the spectra of pure drug. The chemical shift of the AQs bands were measured with reference to the TMS band as internal standard.

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.

Synthesis of anthraquinone drugs

1,5-bis {[2-(methylamino)ethyl]amino}-4,8-dihydroxy anthracene-9,10-dione, (AQ5), and 1,5-bis{[2-(methylamino)ethyl]amino} anthracene-9,10-dione, (AQ5H) were synthesized according to the following method [35–37]:

AQ5H synthesis

1 1,5-dichloroanthraquinone (15 g, 54 mmol) was dissolved in *N*,*N*-dimethylethylenediamine (47.6 g, 540 mmol) and refluxed for 18 h. The reaction was monitored by TLC (9:1 CH_2Cl_2/MeOH). The mixture was cooled to room temperature and diluted with water to precipitate the title compound. The filtered solid was recrystallized from methanol to afford AQ5H (15.8 g, 89%) as a crystalline solid. R_f(9:1 CH_2Cl_2/MeOH): 0.60. ^{1}H NMR δ ($CDCl_3$): 9.8 (t, 2H), 7.6 (m, 4H), 6.9 (m, 2H), 3.4 (q, 4H), 2.7 (t, 4H), 2.4 (s, 12H). Mass spectrum, *m*/*z* 381 ($m^+ + 1$).

AQ5 synthesis

2 The AQ5H (6 g, 15.8 mmol) was dissolved in 65 g of concentrated sulphuric acid and cooled to −10 °C. Anhydrous sodium chlorate (6.5 g, 61.6 mmol) was added in portions over 1.5 h and the mixture then stirred for 3 h at room temperature. The blue solution was added slowly to cold sodium hydrogen sulfite solution (1%, 1000 cm^3). The mixture was neutralised to pH 7 with 5 M sodium hydroxide. The titled compound was extracted from the aqueous phase with CH_2Cl_2 and concentrated. Column chromatography (SiO_2, (9:1 CH_2Cl_2/MeOH) gave AQ5 (1.2 g, 20%). R_f(9:1 CH_2Cl_2/MeOH):0.17. ^{1}H NMR δ ($CDCl_3$): 13.99 (s, 2H), 9.8 (t, 2H), 7.2 (d, 2H), 7.0 (d, 2H), 3.42 (q, 4H), 2.65 (t, 4H), 2.33 (s, 12H). ^{13}C NMR δ ($CDCl_3$): 186.5, 154.9, 137, 135, 115, 114, 58.1, 45.5, 40.95. Mass spectrum, *m*/*z* 413 ($m^+ + 1$). Anal. Calcd. For $C_{22}H_{28}O_4N_4.0.5H_2O$: C, 62.7; H, 6.7; N, 13.3. Found: C, 62.7; H, 6.9; N, 13.3. UV–VIS Lambda max 642, 600, 238.

3. Computations

All computations were done using G09 suit of programs [38]. Molecular geometry of anthraquinone compounds were optimized in the gas phase at DFT B3LYP/6-31 + G(d,p) level of theory. A frequency job was performed on the optimized geometry to confirm a minimum energy structure. Fukui functions were calculated using DMol^3 module [39,40] employing B3LYP/DND method implemented in Material studio program [41].

4. Results and discussion

4.1. Computational work

4.1.1. Molecular geometry

Since there is no reported experimental molecular geometrical data for AQ5 and AQ5H, we calculated the geometry of AQ5, AQ5H and 1,5-DAAQ at B3LYP/6-31 + G(d). Based on possibility of intra molecular hydrogen bonding formation, four minimum energy conformers, Conf-1, Conf-2, Conf-3 and Conf-4, of AQ5 were studied and displayed in Fig. 1. Conf-1 allows four intra-molecular hydrogen bonds while Conf-2 allows three intra-molecular hydrogen bonds and Conf-3 and Conf-4 allow two and one intra molecular hydrogen bonds respectively (see Fig. 1). The relative total energies differences are shown in Fig. 1. Conf-1 with four intra molecular hydrogen bonds is the most stable structure separating from Conf-4, with only one hydrogen bond, by 41.858 kcal/mol. Conf-2 with three hydrogen bonds is the next stable structure with energy difference 15.762 kcal/mol and Conf-3, with two hydrogen bonds, is separating from Conf-1 by 27.045 kcal/mol. Conformer with no intra molecular hydrogen bonds was also studied however, an optimized minimum structure has not been obtained.

Optimized geometry of AQ5 conformers are shown in Fig. 1. All optimized geometrical parameters of AQ5, Conf-1-4, are represented in Tables S1–S4 in the Supplementary Material. Vibrational frequencies for AQ5 Conf-1 were computed to confirm the minimum energy structure and given in Table S5 in Supplementary Materials.

In Conf-1, the carbonyls bond lengths C_7=O_{15} and $C_{10} = O_{16}$ are identical and calculated as 1.273 Å. The reason for being the same

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